



Louisiana

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: KRAS, NRAS and BRAF Mutation Analysis in Metastatic Colorectal Cancer is addressed separately in medical policy 00233.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

BRAF V600E AND/ OR MLH1 PROMOTER METHYLATION

Based on the review of available data, the Company may consider somatic genetic testing for *BRAF* V600E and/or *MLH1* promoter methylation to exclude a diagnosis of Lynch syndrome when *MLH1* protein is not expressed in a colorectal cancer (CRC) tumor on immunohistochemical (IHC) analysis to be **eligible for coverage**.**

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

APC TESTING (FAMILIAL ADENOMATOUS POLYPOSIS)

Based on review of available data, the Company may consider germline genetic testing for adenomatous polyposis coli (APC) gene variants in the following patients to be **eligible for coverage**:**

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- At-risk relatives (first or second degree) of patients with familial adenomatous polyposis (FAP) and/or a known adenomatous polyposis coli (APC) pathogenic variant (single site analysis only); or
- Patients with a differential diagnosis of attenuated familial adenomatous polyposis (FAP) vs. *MUTYH*-associated polyposis (MAP) vs. Lynch syndrome. Whether testing begins with adenomatous polyposis coli (APC) variants or screening for mismatch repair (MMR) variants depends upon clinical presentation.

Notes:

*Genetic testing for adenomatous polyposis (APC and *MUTYH* gene variant analysis) is recommended when an individual has a personal history of 10 or greater cumulative adenoma polyps, or with family history of a known P/LP variant in polyposis genes. Individuals with 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) can also be considered for the APS syndrome assessment.*

Classical FAP (familial adenomatous polyposis) or attenuated FAP (AFAP) are autosomal dominant conditions due to germline P/LP variants in the APC gene. Classical FAP is suspected based on the early onset of at least 100 cumulative adenomas in the large bowel, starting in adolescences. AFAP is characterized by a later onset and fewer cumulative lifetime adenomas (from 10-100).

MUTYH TESTING (MUTYH-ASSOCIATED POLYPOSIS)

Based on the review of available data, the Company may consider germline genetic testing for *MUTYH* gene variants to be **eligible for coverage** ** in the following patients:

- At-risk relatives (first or second degree) with a known *MUTYH* gene variant (single site analysis only), OR
- Patients with a differential diagnosis of attenuated familial adenomatous polyposis (FAP) vs *MUTYH*-associated polyposis (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).

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Policy # 00190

Original Effective Date: 10/16/2006

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Note:

MAP (MUTYH-associated polyposis) follows a recessive pattern of inheritance; MUTYH testing should be considered if colonic polyposis is present only in siblings (parents unaffected). Most individuals with MAP generally have fewer than 100 adenomas (uncommonly > 100).

MMR GENE TESTING (LYNCH SYNDROME/ HEREDITARY NONPOLYPOSIS COLORECTAL CANCER)

Based on the review of available data, the Company may consider germline genetic testing for mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) in the following patients to be **eligible for coverage:****

- Personal history of tumor with MMR deficiency determined by PCR, NGS, or IHC at any age; or
- An individual with colorectal cancer (CRC) or endometrial cancer and ANY of the following:
 - Diagnosed < 50 years
 - Another synchronous or metachronous Lynch Syndrome (LS) related cancer regardless of age
 - 1 first-degree or second-degree relative with an LS-related cancer diagnosed < 50 years
 - ≥2 first-degree or second-degree relatives with Lynch syndrome-related cancers regardless of age
- Family history (on same side of family) of ANY of the following:
 - ≥1 first-degree relative with a CRC or endometrial cancer diagnosed < 50 years
 - ≥1 first-degree relative with a CRC or endometrial cancer and another synchronous or metachronous LS-related cancer regardless of age
 - ≥2 first-degree or second-degree relatives with LS-related cancers including ≥1 diagnosed < 50 years
 - ≥3 first-degree or second-degree relatives with LS-related cancers regardless of age
- At-risk relatives (See Policy Guidelines section) of patients with Lynch syndrome with a known pathogenic/ likely pathogenic MMR gene variant (familial variant single site analysis only); or
- Patients with a differential diagnosis of attenuated familial adenomatous polyposis (FAP) vs. *MUTYH* -associated polyposis (MAP) vs. Lynch syndrome. Whether testing begins with

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Policy # 00190

Original Effective Date: 10/16/2006

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polyposis coli (APC) variants or screening for MMR genes depends upon clinical presentation; or

- Patients without colorectal cancer (CRC) or endometrial cancer, but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome based on a validated risk prediction model (e.g. PREMM5, MMRpro, or MMRpredict), when no affected family members have been tested for MMR variants.

EPCAM TESTING (LYNCH SYNDROME)

Based on the review of available data, the Company may consider germline genetic testing for the epithelial cell adhesion molecule (*EPCAM*) gene variants to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility will be met when **ANY ONE** of the following 3 major criteria (solid bullets) is met:

- Patients with colorectal cancer (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 (MSI) 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 epithelial cell adhesion molecule (*EPCAM*) variant (single site analysis only);
- OR**
- Patients without colorectal cancer (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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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

Notes:

When there is family history of a known pathogenic or likely pathogenic (P/LP) variant in a colorectal polyposis gene, the individual should be tested for the familial pathogenic variant (i.e., single site testing).

When patient selection criteria are met, germline multi-gene testing with panels that include clinically actionable genes associated with Lynch syndrome (i.e., MLH1, MSH2, MSH6, PMS2, and EPCAM), as well as other highly penetrant genes associated with CRC (e.g., APC, MUTYH, SMAD4, BMPR1A, STK11, TP53, PTEN) can be considered when there is no known familial P/LP variant, especially when personal or family history meets criteria for more than one hereditary cancer syndrome.

When appropriate, single code representing panel (i.e., CPT code 81435, with 81436 only if initial sequencing represented by code 81435 did not identify P/LP variants) should be reported rather than multiple codes representing individual or sequential gene testing.

Multi-gene testing is not recommended when the family history is strongly suggestive of a known hereditary cancer syndrome, or the patient is diagnosed with CRC with MSI or loss of one or more DNA MMR proteins (syndrome-specific panel should be done).

SMAD4 AND BMPR1A TESTING (JUVENILE POLYPOSIS SYNDROME)

Based on the review of available data, the Company may consider germline genetic testing for SMAD4 and BMPR1A gene variants to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be met when **ANY ONE** of the following major criteria (solid bullets) is met:

- Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of **ANY ONE** of the following:
 - At least 5 juvenile polyps in the colon; **OR**
 - Multiple juvenile polyps found throughout the gastrointestinal tract; **OR**
 - Any number of juvenile polyps in a person with a known family history of juvenile polyps;

OR

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Policy # 00190

Original Effective Date: 10/16/2006

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- At-risk relative of a patient diagnosed with juvenile polyposis syndrome.

Note:

With JPS, juvenile hamartomatous polyps in the rectosigmoid region usually manifest during childhood (90% of patients present with bleeding and/or anemia). Histologically, polyps are exophytic, eroded, contain marked edema and inflammation within the lamina propria, cystic glands with thick mucin, and some degree of smooth muscle proliferation.

STK11 TESTING (PEUTZ-JEGHERS SYNDROME)

Based on the review of available data, the Company may consider germline genetic testing for STK11 gene variants to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be met when **ANY ONE** of the following major criteria (solid bullets) is met:

- Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of **ANY TWO** of the following:
 - presence of 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;
- OR**
- At-risk relative of a patient diagnosed with Peutz-Jeghers syndrome.

Note:

PJS hamartomatous GI polyps tend to be large and pedunculated and have a characteristic histology showing broad bands of smooth muscle fibers, chronic inflammation, edema, and fibrosis within the lamina propria and dilated glands.

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When Services Are Considered Not Medically Necessary

APC TESTING

Genetic testing for adenomatous polyposis coli (APC) gene variants is **not medically necessary**** for colorectal cancer patients with classical familial adenomatous polyposis (FAP) for confirmation of the FAP diagnosis.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on the review of available data, the Company may consider testing for germline *APC*, *MUTYH*, *MMR*, *EPCAM*, *SMAD4*, *BMPRIA*, and *STK11* gene variants for inherited CRC syndromes to be **investigational*** in all other situations.

Based on the review of available data, the Company may consider testing for somatic *BRAF V600E* and/or *MLH1* promoter methylation to exclude a diagnosis of Lynch syndrome to be **investigational*** in all other situations.

Based on the review of available data, the Company may consider genetic testing of all other genes for an inherited CRC syndrome to be **investigational***, including but not limited to direct-to-consumer genetic testing (e.g., mail or online ordering), mRNA sequence analysis, testing for variants of unknown significance, polygenic risk scores (PRS), and testing large panels of genes (e.g., Myriad myRisk[®]†, CancerNext[®]‡, Comprehensive Common Cancer Panel, Invitae Multi-Cancer Panel, Invitae Common Hereditary Cancers Panel).

When Services Are Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered****.

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Policy # 00190

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Note:

Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline tests include, but are not limited to, single gene testing, gene panel tests, and whole exome or whole genome sequencing for inherited disorders and pharmacogenomic/cytochrome P450 testing.

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 permitted, eg, 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 2 second-degree relatives with a Lynch syndrome-related cancer, including at least 1 diagnosed before 50 years of age, or at least 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. 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 CRC being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test or the IHC test with or without *BRAF* gene variant testing, should be used as an initial evaluation of tumor tissue before 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

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information if MMR genetic testing is inconclusive. 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 are very stringent and outline increased risk for Lynch syndrome in a family with a proband affected by CRC or any other Lynch syndrome (LS)-associated cancer (i.e., endometrial, small bowel, ureter, or renal-pelvic cancers), and three relatives with a LS-associated cancer provided the following family criteria are met (all criteria must be fulfilled):

- 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;
- 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 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.

The Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less stringent than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also considered more useful in identifying which patients with

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

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CRC should have their tumors tested for microsatellite instability (MSI) and/or immunohistochemistry (IHC):

- CRC diagnosed in a patient who is younger than 50 years old;
- Presence of synchronous or metachronous CRC or other HNPCC-associated tumors,^a regardless of age;
- CRC with high microsatellite instability histology (MSI-H histology) diagnosed in a patient younger than 60 years old;
- CRC in a patient with a family history of 1 first-degree relatives with a Lynch syndrome (LS)-associated cancer diagnosed earlier than age 50 years
- CRC in a patient with a family history of 2 or more first or second-degree relatives with LS-associated tumors,^a regardless of age.

^a 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 (Kastrinos et al [2017]), 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.

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.

Background/Overview

Hereditary Colorectal Cancers

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Currently, 2 types of hereditary CRCs are well-defined: 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

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 develop CRC. The 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 extraintestinal manifestations is sometimes referred to as Gardner syndrome. FAP may also be related to central nervous system tumors, referred to as Turcot syndrome.

Germline variants in the *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.

Genetic testing for FAP in at-risk children is recommended to be done no later than age 10 to 15 years, the age at which polyp surveillance would be initiated.

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 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 MAP. MAP 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

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Policy # 00190

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Current Effective Date: 12/11/2023

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 (ie, 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 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 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 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*, *EXO1*) 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.

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Policy # 00190

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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 testing (phenotype): Individuals with high MSI either proceed to genetic testing for *MLH1*, *MSH2*, *MSH6*, and *PMS2* or to 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). 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 the staining of tumor tissue for the presence of 4 MMR proteins (*MLH1*, *MSH2*, *MSH6*, *PMS2*). The absence of one 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. 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 somatic hypermethylation of the *MLH1* promoter. Additionally, some tumors positive for *MSH6* variants are associated with the

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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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 (eg, through frequent colonoscopic or endometrial screening examinations), and prophylaxis (eg, 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. 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 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 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 an *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

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

“epivariants,” ie, 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.

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 (low sensitivity but high specificity), Revised Bethesda guidelines (better sensitivity but poorer specificity), and risk prediction models (eg, 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 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 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.

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

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 *BMPRIA* 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. 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 *BMPRIA* 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

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

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

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 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. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (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. Genetic tests reviewed in this 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. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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).

Summary of Evidence

For individuals who are suspected of attenuated familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis (MAP), and Lynch syndrome who receive genetic testing for adenomatous polyposis coli (*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. 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 2 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 an improvement in the net health outcome.

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, (2) have colon cancer, (3) have endometrial cancer meeting clinical criteria for Lynch syndrome, (4) are at-risk relatives of patients with Lynch syndrome, (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 colorectal cancer (CRC). 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

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

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 an improvement in the net health outcome.

For individuals who warrant Lynch testing, screen negative on MMR testing, but positive for microsatellite instability (MSI) and lack MSH2 protein expression who receive genetic testing for *EPCAM* variants, the evidence includes variant prevalence studies and case series. 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 an improvement in the net health outcome.

For individuals who have CRC in whom MLH1 protein is not expressed on IHC analysis and who receive genetic testing for *BRAF* V600E or *MLH1* promoter methylation, the evidence includes case series. 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 an 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 juvenile polyposis syndrome (JPS) or Peutz-Jeghers syndrome (PJS) who receive genetic testing for *SMAD4*, *BMPRIA*, or *STK11* genes, respectively, the evidence includes multiple observational studies. 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 *BMPRIA* and *STK11* variants with JPS and PJS, respectively. Direct evidence of clinical utility for genetic testing of JPS or PJS is not available. Genetic testing may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

screening programs resulting in psychological relief, and improving 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 an improvement in the net health outcome.

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 colorectal cancer syndromes (v.1.2023) are summarized in Table 1.

Table 1. Criteria for Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer

Criteria for the Evaluation of Lynch Syndrome
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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

Known LS variant in the family
<p>An individual with colorectal or endometrial cancer and any of the following:</p> <ul style="list-style-type: none"> • Diagnosed <50 y • Another synchronous or metachronous LS-related cancer^a regardless of age • 1 first-degree or second-degree relative with LS-related^a cancer diagnosed <50 y • ≥2 first-degree or second-degree relatives with LS-related^a cancers regardless of age
Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age ^b
<p>Family history (on the same side of the family) of any of the following:</p> <ul style="list-style-type: none"> • ≥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^a • ≥2 first-degree or second-degree relatives with LS-related cancer,^a including ≥1 diagnosed <50 y • ≥3 first-degree or second-degree relatives with LS-related cancers,^a regardless of age
<p>An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (ie, PREMM5, MMRpro, MMRpredict)</p> <ul style="list-style-type: none"> • 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.

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

^a LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, urothelial, 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, urothelial, 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.

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

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 post surgery 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 2 and 3.

Table 2. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome

Site	Lifetime Risk, %	Screening Procedure and Interval	Approximate Initiation Age, y
Breast	32 to 54	<ul style="list-style-type: none">Mammogram and breast MRI annuallyClinical 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

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Louisiana

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

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	Annual imaging of the pancreas with either EUS or MRI/MRCP (both ideally performed at center of expertise)	30 to 35 y ^a
Cervix (typically minimal deviation adenocarcinoma)	≥10	<ul style="list-style-type: none">• Pelvic examination and Pap smear annually• Consider total hysterectomy (including uterus and cervix) once completed with childbearing	18 to 20 y
Uterus	9	<ul style="list-style-type: none">• Annual pelvic examination with endometrial biopsy if abnormal bleeding	18 to 20 y
Ovary (sex cord tumor with annular tubules)	≥20	<ul style="list-style-type: none">• Annual pelvic examination with annual pelvic ultrasound	18 to 20 y
Lung	7 to 17	<ul style="list-style-type: none">• Provide education about symptoms and smoking cessation• No other specific recommendations have been made	<ul style="list-style-type: none">•

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

Testes (Sertoli cell tumors)	9	<ul style="list-style-type: none"> Annual testicular exam and observation for feminizing changes 	Continued from pediatric screening
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CT: computed tomography; EUS: endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging.

^aBased on clinical judgment, early initiation age may be considered, such as 10 y younger than the earliest age of onset in the family.

Table 3. Pediatric and Adult Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome

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

HHT: hereditary hemorrhagic telangiectasia;

^a If polyp burden or polyp-related symptoms (ie, 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

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

involvement, *BMP1A* 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 *BMP1A* 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.

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.

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.”

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

For juvenile polyposis syndrome, the College recommended:

“Genetic evaluation of a patient with possible JPS [juvenile polyposis syndrome] should include testing for *SMAD4* and *BMPRIA* 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). The recommendations as related to genetic testing hereditary CRC syndromes are summarized below:

- “Tumor testing ***for DNA mismatch repair (MMR) deficiency*** with immunohistochemistry for MMR proteins and/or MSI should be ***assessed*** in all CRC patients. As an alternate

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Current Effective Date: 12/11/2023

strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines.

- 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 (eg, 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 (ie, 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.

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Current Effective Date: 12/11/2023

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

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

NCT: national clinical trial.

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Policy History

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

04/05/2006	Medical Director review
04/19/2006	Medical Policy Committee review
06/13/2007	Medical Director review
06/20/2007	Medical Policy Committee approval. Added statement to consider investigational when patient selection criteria are not met.
10/10/2007	Medical Director review
10/17/2007	Medical Policy Committee approval. No change to policy statement.
10/01/2008	Medical Director review

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy # 00190

Original Effective Date: 10/16/2006

Current Effective Date: 12/11/2023

10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee review
10/14/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Policy revised extensively.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Committee approval. Policy revisions include the addition of Amsterdam II Clinical Criteria and Revised Bethesda Guidelines for defining risk for Lynch Syndrome.
01/23/2013	Coding updated
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. Policy title revised from "Genetic Testing for Inherited Susceptibility to Colon Cancer Including Microsatellite Instability Testing" to "Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes" since Lynch syndrome is not a polyposis syndrome. Added that BRAF V600E or MLH1 promoter methylation may be considered eligible for coverage when MLH1 is not expressed in the tumor on IHC analysis. Added that testing for all other gene mutations for Lynch syndrome or colorectal cancer is considered investigational.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Added the words "a patient with" to the guidelines.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Bethesda Guidelines clarified. Added to eligibility statement for MMR gene mutation testing "Patients with $\geq 5\%$ risk of Lynch Syndrome on one of the following mutation prediction models: MMRpro, PREMM1,2,6, or MMRpredict."
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016	Coding update

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04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. No changes to coverage eligibility.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. No changes to coverage eligibility.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. No changes to coverage eligibility.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. Guidelines updated.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Policy section revised to add policy statements indicating that genetic testing for SMAD4, BMPR1A, or STK11 gene variants may be considered eligible for juvenile polyposis syndrome and Peutz-Jeghers syndrome.
06/17/2019	Coding update
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Policy statements for MMR and EPCAM testing revised for to include criteria for individuals with documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model (e.g. MMRpro, PREMM5 or MMRpredict) are eligible for genetic testing.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Policy statements on juvenile polyposis syndrome and Peutz-Jeghers syndrome updated with revised NCCN diagnostic criteria.
12/11/2020	Coding update
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. No change to coverage.
03/25/2022	Coding update
11/03/2022	Medical Policy Committee review

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- 11/09/2022 Medical Policy Implementation Committee approval. Extensively revised due to Senate Bill update.
- 11/02/2023 Medical Policy Committee review
- 11/08/2023 Medical Policy Implementation Committee approval. Removed “on the same side of the family” from the first or second degree relative bullet coverage statement for Lynch Syndrome/ Hereditary Nonpolyposis Colorectal Cancer. Note clarified by adding “gene variant analysis” and “Individuals with 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) can also be considered for the APS syndrome assessment.” Added When Services are not covered section for repeat germline testing and note to the policy. Policy guidelines added “a 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.”

Next Scheduled Review Date: 11/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)[†], copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0101U, 0130U, 0238U, 81201, 81202, 81203, 81210, 81288, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81317, 81318, 81319, 81405, 81406, 81435, 81436 Delete codes effective 01/01/2023: 81355, 81455 Add codes effective 12/01/2023: 81401, 81403
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with evaluation center(s);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: 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 eligibility for coverage.

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