BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

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

Annual Effective Policy Date: January 1, 2026

Original Policy Date: March 2012

Related Policies:

2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, NTRK, RET and HER2)
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Description

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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).

OBJECTIVE

The objective of this evidence review is to assess whether the use of genetic testing improves the net health outcome in patients with Lynch syndrome and other inherited colon cancer syndromes.

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POLICY STATEMENT

APC Testing

Genetic testing of the *APC* gene 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.
- Individuals with a differential diagnosis of attenuated FAP versus *MUTYH*-associated polyposis (MAP) versus 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 considered **not medically necessary** for colorectal cancer (CRC) 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.

MUTYH Testing

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

- Individuals with a differential diagnosis of attenuated FAP versus MAP versus 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.

MMR Gene Testing

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

- 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 versus MAP versus 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.

EPCAM Testing

Genetic testing of the *EPCAM* gene may be considered **medically necessary** when any 1 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 individual is negative for an *MSH2* germline variant; OR
    - Tumor tissue shows a high level of microsatellite instability and individual is negative for a germline variant in *MLH1*, *MSH2*, *MSH6*, and *PMS2*; OR

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- At-risk relatives (see Policy Guidelines section) of individuals with Lynch syndrome with a known pathogenic/likely pathogenic *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.

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

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.

SMAD4 and *BMPR1A* Testing

Genetic testing of *SMAD4* and *BMPR1A* genes may be considered **medically necessary** when any 1 of the following major criteria (solid bullets) is met:

- Individuals with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any 1 of the following:
    - at least 5 juvenile polyps in the colon.
    - multiple juvenile polyps found throughout the gastrointestinal tract.
    - any number of juvenile polyps in a person with a known family history of juvenile polyps.
- At-risk relative of anindividual 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.

STK11 Testing

Genetic testing for *STK11* gene variants may be considered **medically necessary** when any 1 of the following major criteria (solid bullets) is met:

- Individuals with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 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.
- At-risk relative of anindividual suspected of or diagnosed with Peutz-Jeghers syndrome.

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

Other Variants

Genetic testing of all other genes for an inherited CRC syndrome is considered **investigational**.

Genetic Counseling

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

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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. 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 (FAP) or Lynch syndrome be performed in an affected family member, so that testing in unaffected family members can focus on the variant found in the affected family member (see Benefit Application section). If an affected family member is not available for testing, testing should begin with an unaffected family member most closely related to an affected family member.

In many cases, genetic testing for *MUTYH* gene variants should first target the specific variants *Y165C* and *G382D*, which account for more than 80% of variants in white populations, and subsequently, proceed to sequence only as necessary. However, in other ethnic populations, proceeding directly to sequencing is appropriate.

Evaluation for Lynch Syndrome

For patients with colorectal cancer (CRC) or endometrial cancer being evaluated for Lynch syndrome, the microsatellite instability (MSI) test or the immunohistochemical (IHC) test with or without *BRAF* gene variant testing, or methylation testing, should be used as an initial evaluation of tumor tissue before mismatch repair (MMR) gene analysis. Both tests are not necessary. Proceeding to MMR gene sequencing would depend on the results of MSI or IHC testing. In particular, IHC testing may help direct which MMR gene likely contains a variant, if any, and may also provide additional information if MMR genetic testing is inconclusive. 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.

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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FDA REGULATORY STATUS

This policy also assumes that the microsatellite instability test or the immunohistochemical test as an initial evaluation for Lynch syndrome is performed as part of the routine pathologic evaluation of the colorectal or endometrial cancer specimen. Thus, this policy deals only with testing for genetic variants. Proceeding to DNA mismatch repair gene sequencing would depend on the results of microsatellite instability and immunohistochemical testing. Microsatellite instability and immunohistochemical testing may also provide additional information when genetic testing for nonpolyposis colorectal cancer is inconclusive.

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

RATIONALE

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 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 immunohistochemical (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.

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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*, *BMPR1A*, 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 *BMPR1A* 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 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

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.

American College of Gastroenterology

The American College of Gastroenterology (2015) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.[21,]

For Lynch syndrome, the College recommended:

"All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair [MMR] deficiency.

Analysis may be done by immunohistochemical [IHC] testing for the *MLH1/MSH2/MSH6/PMS2* proteins and/or testing for microsatellite instability [MSI]. 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 MMR deficiency (and no demonstrated BRAF variant or hypermethylation of *MLH1),* a known family variant associated with LS [Lynch syndrome], or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.[78,]

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

For adenomatous polyposis syndromes, the College recommended:

"Familial adenomatous polyposis (FAP)/MUTYH-associated polyposis/attenuated polyposis

Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of 1one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes.

Genetic testing of patients with suspected adenomatous polyposis syndromes should include *APC* and *MUTYH* gene variant analysis."

For juvenile polyposis syndrome, the College recommended*:*

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

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

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

Cardiovascular examination for and evaluation for hereditary hemorrhagic telangiectasia should be considered for *SMAD4* mutation carriers (conditional recommendation, very low quality of evidence)."

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For Peutz-Jeghers syndrome, the College recommended:

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

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

American Society of Clinical Oncology and Society of Surgical Oncology

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

- "Tumor testing ***for DNA MMR deficiency*** with IHC for MMR proteins and/or MSI should be ***assessed*** in all CRC patients. As an alternate 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***."

National Comprehensive Cancer Network

The NCCN guidelines on genetic/familial high-risk assessment of colorectal cancer syndromes (v1.2025v2.2023) are summarized in Table 1.[80,]

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

Criteria for the Evaluation of Lynch Syndrome
Known LS pathogenic variant in the family
An individual with a LS-related cancer and any of the following: • Diagnosed <50 y • Another synchronous or metachronous LS-related cancer[a] regardlesss 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]
Family history (on the same side of the family) of any of the following: • ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 y • ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer[a] • ≥2 first-degree or second-degree relatives with LS-related cancer,[a] including ≥1 diagnosed <50 y

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- ≥3 first-degree or second-degree relatives with LS-related cancers,[a] regardless of age

An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict)

- Individuals with a personal history of CRC and/or endometrial cancer with a $PREMM_5$ 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 $PREMM_5$ 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: immunohistochemisty; LS: Lynch syndrome; MGPT: multi-gene panel testing; MMR: mismatch repair; MSI: microsatellite instability; NGS: next generation sequencing; PCR: polymerase chain reaction.

[a] LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, 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 MMR using IHC and/or MSI is used to identify which patients should undergo mutation testing for Lynch syndrome.[81,] 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 (v4.2024) recommend that all newly diagnosed patients with colon cancer be tested for MMR or MSI.[26,]

The NCCN guidelines for uterine neoplasm (v2.2024)also recommend universal screening for MMR genes (and MSI testing if results are equivocal).[27,] 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 (v2.2023) recommend genetic testing for at-risk family members of patients with positive variants in *MLH1*, *MSH2*, *MSH6*, *PMS2, and EPCAM*.[80,] These guidelines also address familial adenomatous polyposis (classical and attenuated) and *MUTYH*-associated polyposis and are consistent with the information provided in this evidence review.

Surveillance Recommendations for Lynch Syndrome

The NCCN guidelines for colon cancer (v4.2024)[26,] and for colorectal cancer (CRC) screening (v1.2024)[81,] recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year postsurgery and, if normal, again in 3 years, then every 5 years based on findings.

The NCCN guidelines on genetic/familial high-risk assessment for CRC indicate for MLH1, MSH2, and EPCAM variant carriers that surveillance with colonoscopy should begin "at age 20 to 25 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years."[80,]

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". [80,]

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.[80,]

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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	• Mammogram and breast MRI annually • Clinical breast exam every 6 mo	30 y
Colon	39	Colonoscopy every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology	18 y
Stomach	29	Upper endoscopy every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology	18 y
Small intestine	13	Small bowel visualization (CT or MRI enterography or video capsule endoscopy) every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology	18 y
Pancreas	11 to 36	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	• Pelvic examination and Pap smear annually • Consider total hysterectomy (including uterus and cervix) once completed with childbearing	18 to 20 y
Uterus	9	• Annual pelvic examination with endometrial biopsy if abnormal bleeding	18 to 20 y
Ovary (sex cord tumor with annular tubules)	≥20	• Annual pelvic examination with annual pelvic ultrasound	18 to 20 y
Lung	7 to 17	• Provide education about symptoms and smoking cessation • No other specific recommendations have been made	
Testes (Sertoli cell tumors)	9	• Annual testicular exam and observation for feminizing changes	Continued from pediatric screening

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

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

Site	Lifetime Risk, % for *SMAD4/BMPR1A* variants	Screening Procedure and Interval	Approximate Initiation Age, y
Colon	up to 50	Adults: Colonoscopy every 1 - 3 years. Intervals should be based on polyp size, number, and pathology[a] Pediatrics: Colonoscopy every 2 - 3 years. Intervals should be based on polyp size, number, and pathology[a]	Adults: 18 y Pediatric: 12-15 y
Stomach	up to 21, especially if multiple gastric polyps present	Adults:Upper endoscopy every 1 - 3 years. Intervals should be based on polyp size, number, and pathology.[a,b] Pediatrics: Upper endoscopy and polypectomy every 2 - 3 years. Intervals should be based on polyp size, number, and pathology[a]	Adults: 18 y Pediatric: 12-15 y
Small intestine	Rare, undefined	No recommendations made	
HHT	22	In individuals with *SMAD4* variants, screen for vascular lesions associated with HHT	Within first 6 mo of life, or at time of diagnosis

HHT: hereditary hemorrhagic telangectasia.

[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 involvement, BMRP1A pathogenic variant carriers may have a less severe upper gastrointestinal tract phenotype and may merit lengthened surveillance intervals in the absence of polyps. Gastric cancer risk for BMPR1A pathogenic variant carriers may be lower than for SMAD4 pathogenic variant carriers

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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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2012	New policy	
March 2013	Replace policy	Policy updated with name change and literature review; References 15, 30, 43-49, 52, 53 added. Additional medically necessary indication added for patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer.
March 2014	Replace policy	Updated with literature review through September 2013. References 24, 33-35 and 58 added. References 39-40 updated. Policy Statement added that BRAF V600E or MLH1 promoter methylation may be considered medically necessary when MLH1 is not expressed in the tumor on IHC analysis.
December 2016	Replace policy	Policy updated with literature review through December 29, 2015; references 59-60 added. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through July 21, 2017; references 4-6, 28-33, 35-39, 41, 51-57, 64-65, 67-70, 83 added.
December 2018	Replace policy	Policy updated with literature review through July 9, 2018; references 22-36 and 92-99 added. Policy section revised to add policy statements indicating that genetic testing for SMAD4, BMPR1A, or STK11 gene variants may be considered medically necessary for juvenile polyposis syndrome and Peutz-Jeghers syndrome. Information related to "at-risk relatives€š deleted due to benefit considerations.
December 2019	Replace policy	Policy updated with literature review through August 6, 2019; references on NCCN updated. Clarification added to objective statement "This review does not address individuals without a personal history of cancer, nor screening or presymptomatic use of genetic tests and services."
December 2020	Replace policy	Policy updated with literature review through July 31, 2020; references on NCCN updated. Policy statements on juvenile polyposis syndrome and Peutz-Jeghers syndrome updated with revised NCCN diagnostic criteria. The intent of the policy statements is unchanged.
December 2021	Replace policy	Policy updated with literature review through August 10, 2021; references on NCCN updated and reference added. Policy statements on MMR gene testing clarified "with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome"; the intent of the policy is unchanged. The MUTYH and BRAF V600E or MLH1 Promoter Methylation policy statements added that all other situations are considered investigational.
December 2022	Replace policy	Policy updated with literature review through July 18, 2022; references added. Policy statements unchanged.
December 2023	Administrative correction	Policy corrected to add Dec. 2019 objective language inadvertently omitted from the Dec 2022 update: This review does not address individuals without a personal history of cancer, nor screening or presymptomatic use of genetic tests and services."
December 2024	Replace policy	Policy updated with literature review through July 15, 2024; no references added. Policy statements unchanged.
December 2025	Replace policy	Policy updated with literature review through August 5, 2025; no references added. Policy statements unchanged.

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