PHP_2.04.08	Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes		
Original Policy Date:	February 1, 2026	**Effective Date:**	February 1, 2026
Section:	2.0 Medicine	**Page:**	Page 1 of 37

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. DHCS Provider Manual Guideline:
- Pathology: Molecular Pathology

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing
Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test.

Biomarker Testing
Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

Pharmacogenomic Testing
Pharmacogenomic testing is defined as a laboratory genetic testing that includes, but is not limited to, a panel test to identify how a person's genetics may impact the efficacy, toxicity and safety of medications. Medically necessary pharmacogenomic testing is covered subject to utilization controls and evidence-based clinical practice guidelines.

Requirements for *APC* (CPT code 81202):

- Requires documentation on the TAR of a family history of familial adenomatous polyposis that includes a relative with a known deleterious APC mutation

Requirements for *MLH1*; promoter methylation analysis (CPT code 81288):

- Document the following criteria on the TAR:
  - Member with cancer(s) associated with Lynch Syndrome, and
  - The tumor demonstrates microsatellite instability or immunohistochemistry results indicating loss of MLH1 protein expression

Requirements for *MLH1*; known familial variants (CPT code 81293):

- Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious MLH1 mutation

Requirements for *MSH2* (CPT code 81296):

- Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious MSH2 mutation

Requirements for *MSH6* (CPT code 81299):

- Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious MSH6 mutation

Requirements for CPT code MSI (Microsatellite instability analysis) 81301:

- Reimbursable for members who meet one of the following criteria: the member is diagnosed with one of the Lynch syndrome-associated cancers; or, the member is diagnosed with an unresectable or metastatic solid tumor and the treatment will be contingent on the test result.

Requirements for *PMS2* (CPT code 81318):

- Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious PMS2 mutation

Requirements for *EPCAM* (CPT code 81403):

- EPCAM (Lynch syndrome) – The member has one of the following:
  - Colon cancer
  - Uterine cancer
  - Lynch syndrome
  - Family history of colorectal cancer, uterine cancer or Lynch syndrome
  - Presence of synchronous, metachronous colorectal or other Lynch-associated tumors

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:

- APL 22-010 – Cancer Biomarker Testing

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the

likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:

- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

Policy Statement

Any criteria that are not specifically addressed in the above APL and Provider Manual, please refer to the criteria below.

APC Testing

I. Genetic testing of the *APC* gene may be considered **medically necessary** in the following individuals with **any** of the following:
   A. At-risk relatives (see Policy Guidelines section) of individuals with familial adenomatous polyposis (FAP) and/or a known *APC* variant ***(Per Medi-Cal guidelines and for Medi-Cal members only: documentation of a family history of familial adenomatous polyposis that includes a relative with a known deleterious APC mutation)***
   B. 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

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

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

MUTYH Testing

IV. Genetic testing of the *MUTYH* gene may be considered **medically necessary** for individuals* with **all** of the following:
   A. Differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome
   B. A negative result for *APC* gene variants

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

MMR Gene Testing

VI. Genetic testing of MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) may be considered **medically necessary** in the following individuals with **any** of the following:
   A. Individuals with CRC with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome (see Policy Guidelines section)
   B. Individuals with endometrial cancer with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome (see Policy Guidelines section)

C. At-risk relatives (see Policy Guidelines section) of individuals with Lynch syndrome with a known pathogenic/likely pathogenic MMR gene variant
D. 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
E. 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

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

EPCAM Testing

VIII. Genetic testing of the *EPCAM* gene may be considered **medically necessary** when **any** 1 of the following 3 major criteria is met:
A. Individuals with CRC, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when:
1. Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and individual is negative for an *MSH2* germline variant
2. Tumor tissue shows a high level of microsatellite instability and individual is negative for a germline variant in *MLH1*, *MSH2*, *MSH6*, and *PMS2*
B. At-risk relatives (see Policy Guidelines section) of individuals with Lynch syndrome with a known pathogenic/likely pathogenic *EPCAM* variant
C. 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

(Per Medi-Cal guidelines and for Medi-Cal members only: the member has one of the following: colon cancer; uterine cancer; Lynch syndrome; family history of colorectal cancer, uterine cancer, or Lynch syndrome; presence of synchronous, metachronous colorectal or other Lynch-associated tumors)

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

BRAF V600E or *MLH1* promoter methylation

X. 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. ***(Per Medi-Cal guidelines and for Medi-Cal members only: For MLH1 promoter methylation testing, the tumor demonstrates microsatellite instability or immunohistochemistry results indicating loss of MLH1 protein expression)***

XI. 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

XII. Genetic testing of *SMAD4* and *BMPR1A* genes may be considered **medically necessary** when any 1 of the following major criteria is met:
A. Individuals with a clinical diagnosis of juvenile polyposis syndrome based on the presence of **any** 1 of the following:
1. At least 5 juvenile polyps in the colon

2. Multiple juvenile polyps found throughout the gastrointestinal tract
3. Any number of juvenile polyps in a person with a known family history of juvenile polyps

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

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

STK11 Testing

XIV. Genetic testing for *STK11* gene variants may be considered **medically necessary** when **any** 1 of the following major criteria is met:
   A. Individuals with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of **any** 2 of the following:
      1. Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the gastrointestinal tract
      2. Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
      3. Family history of Peutz-Jeghers syndrome
   B. At-risk relative of an individual suspected of or diagnosed with Peutz-Jeghers syndrome

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

Other Variants

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

Genetic Counseling

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

Policy Guidelines

MUTYH Testing

*A family history of no parents or children with FAP is consistent with MAP (autosomal recessive)

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, e.g., 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.

The Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent for defining families at high risk for Lynch syndrome [Vasen et. al., 1999; PMID 10348829]:

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

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. [Umar et. al., 2004; PMID 14970275] The Bethesda guidelines are also considered more useful in identifying which patients with CRC should have their tumors tested for MSI and/or 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 MSI histology diagnosed in a patient younger than 60 years old;
- CRC diagnosed in 1 or more first-degree relatives with a Lynch syndrome-associated tumor, with 1 of the cancers being diagnosed before 50 years of age;
- CRC diagnosed in 2 or more first or second-degree relatives with HNPCC-related 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 , or MMRpredict. National Comprehensive Cancer Network guidelines recommend (category 2A) testing for Lynch syndrome in individuals with a 5% or higher predicted risk of the syndrome on these risk prediction models.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

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

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

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

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

Genetic Counseling

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

Coding

See the Codes table for details.

Description

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

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 Technology Evaluation Center (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.

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.

Additional Information
Not applicable.

Related Policies

- N/A

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09
California laws that requires insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview
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.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

Hereditary Colorectal Cancers

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

Familial Adenomatous Polyposis and Associated Variants

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

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

A subset of FAP patients may have an attenuated form of FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP. In the attenuated form of FAP, CRC occurs at an average age of 50 to 55 years, but the lifetime risk of CRC remains high (>70% by age 80 years). The risk of extraintestinal cancer is also lower but cumulative lifetime risk remains high (>38%) compared with the general population.[1] Only 30% or fewer of attenuated FAP patients have *APC* variants; some of these patients have variants in the *MUTYH* (formerly *MYH*) gene, and this form of the condition is called *MUTYH*-associated polyposis (MAP). This form of polyposis occurs with a frequency similar to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic *MUTYH* variants are associated with a cumulative CRC risk of about 80% by age 70, whereas the monoallelic *MUTYH* variant-associated risk of CRC appears to be relatively minimal, although still under debate.[2] Thus, inheritance for high-

risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (i.e., between 10 and 99) adenomas are present, and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include *APC*, *MUTYH* if *APC* is negative for variants, and screening for variants associated with Lynch syndrome.

It is important to distinguish between classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary by syndrome.[3]

Testing

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

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

Lynch Syndrome

Lynch syndrome is an inherited disorder that results in a higher predisposition to CRC and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3% to 5% of all CRC. People with Lynch syndrome have a 70% to 80% lifetime risk of developing any type of cancer.[4,5] However, the risk varies by genotype. It occurs as a result of germline variants in the mismatch repair (MMR) genes that include *MLH1, MSH2, MSH6*, and *PMS2*. In approximately 80% of cases, the variants are located in the *MLH1* and *MSH2* genes, while 10% to 12% of variants are located in the *MSH6* gene, and 2% to 3% in the *PMS2* gene. Additionally, variants in 3 additional genes (*MLH3, PMS1*, *EX01*) have been implicated with Lynch Syndrome. Notably, in individuals meeting the various clinical criteria for Lynch syndrome, 50% of individuals have a variant in the *MLH1, MSH2, MSH6*, and *PMS2* genes. The lifetime risk of CRC is nearly 80% in individuals carrying a variant in 1 of these genes.

Testing

Preliminary screening of tumor tissue does not identify MMR gene variants but is used to guide subsequent diagnostic testing via DNA analysis for specific variants. Genetic testing or DNA analysis (gene sequencing, deletion, and duplication testing) for the MMR genes involves assessment for *MLH1*, *MSH2*, *MSH6*, and *PMS2* variants. The following are 3 testing strategies.

- Microsatellite instability (MSI) testing (phenotype): Individuals with high MSI either proceed to genetic testing for *MLH1*, *MSH2*, *MSH6*, and *PMS2* or to immunohistochemical (IHC) testing.
- IHC testing (phenotype): Individuals with negative staining would proceed to genetic testing for *MLH1*, *MSH2*, *MSH6*, and *PMS2*.
- Modification strategy: Tumor tissue of patients with negative staining for *MLH1* on IHC is tested for the *BRAF* V600E variant to determine methylation status. If the *BRAF* variant is not detected, the individual receives *MLH1* DNA analysis.

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

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

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

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

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

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

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

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

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

Population Selection

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

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

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant genetic disorder characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract. It is rare, with an estimated incidence of 1 in 100,000 to 160,000. Generalized JPS refers to polyps in the upper and lower gastrointestinal tract, and juvenile polyposis coli refers to polyps of the colon and rectum. Those with JPS are at a higher risk for CRC and gastric cancer.[17] Approximately 60% of patients with JPS have a germline variant in the *BMPR1A* gene or the *SMAD4* gene.[18,19] Approximately 25% of patients have de novo variants.[20,21] In most cases, polyps appear in the first decade of life and most patients are symptomatic by age 20 years.[22] 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.[17,21,22]

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.[23,24] The estimated lifetime risk of gastric cancer is 20% to 30%, with a mean age at diagnosis of 58 years.[17,21,23] Juvenile polyposis syndrome may also be associated with hereditary hemorrhagic telangiectasia.[25] The most common clinical manifestations of hereditary hemorrhagic telangiectasia are telangiectasias of the skin and buccal mucosa, epistaxis, and iron deficiency anemia from bleeding.

Diagnosis

A clinical diagnosis of JPS is made on the basis of the presence of any 1 of the following: at least 5 juvenile polyps in the colon or multiple juvenile polyps in other parts of the gastrointestinal tract or any number of juvenile polyps in a person with a known family history of juvenile polyps.[26] It is recommended that individuals who meet clinical criteria for JPS undergo genetic testing for a germline variant in the *BMPR1A* and *SMAD4* genes for a confirmatory diagnosis of JPS and to counsel at-risk family members. If there is a known *SMAD4* variant in the family, genetic testing

should be performed within the first 6 months of life due to hereditary hemorrhagic telangiectasia risk.[27]

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is also an autosomal dominant genetic disorder, similar to JPS, and is characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and nongastrointestinal cancers. It is rare, with an estimated incidence of 1 in 8000 to 200,000. In most cases, a germline variant in the *STK11* (*LKB1*) gene is responsible for PJS, which has a high penetrance of over 90% by the age of 30 years.[28,29,30] However, 10% to 20% of individuals with PJS have no family history and are presumed to have PJS due to de novo variants.[31] A variant in *STK11* is detected in only 50% to 80% of families with PJS, suggesting that there is a second PJS gene locus.

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

Diagnosis

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

Literature Review

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

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

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

Clinical Context and Test Purpose

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

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

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

Populations

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

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

Comparators
The following practice is currently being used to make decisions about managing FAP and MAP: no genetic testing.

Outcomes
The potential beneficial outcomes of primary interest would be the early detection of colorectal cancer (CRC) and appropriate and timely interventional strategies (e.g., endoscopic resection, colectomy) to prolong life.

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

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

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

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

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

Review of Evidence
The evidence review for FAP genetic testing was initially informed by a TEC Assessment (1998).[33] Additional information on attenuated FAP and on MAP diagnostic criteria and genetic testing is based on several publications that build on prior, cited research.[34,35,36,37]

Clinical sensitivity for classic FAP is about 95%; about 90% of pathogenic variants are detected by sequencing,[38,39] while 8% to 12% of pathogenic variants are detected by deletion and duplication testing.[40,41] Among Northern European whites, 98% of pathogenic *MUTYH* variants are detected by full gene sequencing.[42,43]

A comprehensive review of the *APC* pathogenic variant and its association with classical FAP and attenuated FAP and MAP is beyond the scope of this evidence review. The likelihood of detecting an *APC* pathogenic variant is highly dependent on the severity of colonic polyposis[40,44,45,46] and family history.[47] Detection rates are higher in classic polyposis (88%) than in nonclassical FAPs such as attenuated colonic phenotypes (57%) or MAP (33%).

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

Direct Evidence

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

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

Chain of Evidence

Genetic testing of patients requiring a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome may have clinical utility:

- If the test supports the clinical diagnosis of an attenuated disease, the protocol for endoscopic surveillance is affected and, depending on the situation, may avoid more frequent but unnecessary surveillance or necessitates more frequent surveillance.

Genetic testing of at-risk relatives of patients with FAP and/or a known *APC* variant may have clinical utility:

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

A TEC Assessment (1998)[33] offered the following conclusions:

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

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

Section Summary: Genetic Testing for Familial Adenomatous Polyposis and *MUTYH*-Associated Polyposis

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

Lynch Syndrome and Colorectal Cancer Genetic Testing

Clinical Context and Test Purpose

The purpose of genetic testing for Lynch syndrome is to:

- Detect Lynch syndrome in individuals diagnosed with CRC or endometrial cancer,
- Identify at-risk relatives of individuals with a diagnosed Lynch syndrome and/or a known mismatch repair (MMR) variant and/or positive family history meeting Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model,
- Make a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome.

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

Populations

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

Interventions

The relevant intervention is genetic testing for the *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, and/or *BRAF* V600E genes. Commercial testing is available from numerous companies.

Comparators

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

Outcomes

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

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

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

Study Selection Criteria

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

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

Clinically Valid

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

Review of Evidence

MMR Genes

Microsatellite instability (MSI) and immunohistochemical (IHC) screening tests for MMR variants have similar sensitivity and specificity. Microsatellite instability screening has a sensitivity of about 89%

for *MLH1* and *MSH2* and 77% for *MSH6* and a specificity of about 90% for all. IHC screening has sensitivity for *MLH1*, *MSH2*, and *MSH6* of about 83% and a specificity of about 90% for each.

The evidence for Lynch syndrome genetic testing in patients with CRC is based on an evidence report conducted for the Agency for Healthcare Research and Quality by Bonis et al (2007),[48] a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009),[9] and an EGAPP recommendation (2009) for genetic testing in CRC.[49] Based on the Agency for Healthcare Research and Quality report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for MMR variants in patients already diagnosed with CRC:

- Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for MMR variant testing and should not be used as a sole determinant or screening test.
- Optional *BRAF* testing can be used to reduce the number of patients who are negative for *MLH1* expression by IHC, needing *MLH1* gene sequencing, thus improving efficiency without reducing sensitivity for MMR variants.

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

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

EPCAM Testing

Several studies have characterized *EPCAM* deletions, established their correlation with the presence of *EPCAM-MSH2* fusion messenger RNAs (apparently nonfunctional) and with the presence of *MSH2* promoter hypermethylation, and, most importantly, have shown the cosegregation of these *EPCAM* variants with Lynch-like disease in families.[11,52,53,54,55,56] Because studies differ slightly in how patients were selected, the prevalence of these *EPCAM* variants is difficult to estimate but may be in the range of 20% to 40% of patients/families who meet Lynch syndrome criteria, do not have an MMR variant, but have MSI-high tumor tissue. Kempers et al (2011) reported that carriers of an *EPCAM* deletion had a 75% (95% CI, 65% to 85%) cumulative risk of CRC by age 70 years, which did not differ significantly from that of carriers of an *MSH2* deletion (77%; 95% CI, 64% to 90%). The mean age at diagnosis was 43 years.[57] However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0% to 27%) by age 70 compared with carriers of an *MSH2* variant (51%; 95% CI, 33% to 69%; p<.001).

BRAF V600 or MLH1 Promoter Methylation

Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients.[58] MLH1 and PMS2 protein stains were absent in 65 patients who were subsequently tested for a *BRAF* variant. Thirty-six

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

Clinically Useful

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

Direct Evidence

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

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

Chain of Evidence

Genetic testing of patients with colon or endometrial cancer to detect Lynch syndrome has clinical utility:

- To make decisions about the preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis or segmental colectomy).

Genetic testing of at-risk relatives of patients with Lynch syndrome and/or a known MMR variant and/or positive family history meeting Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model, has clinical utility:

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

Genetic testing of patients requiring a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome may have clinical utility:

- If the test supports the clinical diagnosis of Lynch syndrome, the protocol for endoscopic surveillance is affected and, depending on the situation, may avoid more frequent but unnecessary surveillance or necessitates more frequent surveillance.

A chain of evidence can be constructed for the clinical utility of testing all patients with CRC for MMR variants. EGAPP conclusions are summarized next.

- Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients.[61,62,63,64,65,66,67] About half of the relatives received counseling, and 95% of them chose MMR gene variant testing. Among those positive for MMR gene variants, uptake of colonoscopic surveillance beginning at age 20 to 25 years was high at 53% to 100%.

  - One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance versus those who did not.
  - Surveillance and prevention for other Lynch syndrome cancers.
- The chain of evidence from descriptive studies and expert opinion is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., the index patient).
  - Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.
  - Surveillance and prevention for other Lynch syndrome cancers:
    - While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In a retrospective study by Schmeler et al (2006), 315 women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.[68]
    - In a study by Bouzourene et al (2010), surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown.[10] Transvaginal ultrasound is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, transvaginal ultrasound in conjunction with endometrial biopsy has been recommended for surveillance.
    - Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supporting evidence.

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

The risk of endometrial cancer in MMR variant carriers has been estimated at 34% (95% CI, 17% to 60%) by age 70, and at 8% for ovarian cancer (95% CI, 2% to 39%) by age 70.[71] Risks do not appear to appreciably increase until after age 40. Females with Lynch syndrome who choose risk-reducing surgery are encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. In a retrospective cohort study, Obermair et al (2010) found that hysterectomy improved survival among female colon cancer survivors with Lynch syndrome.[72] This study estimated that, for every 100 women diagnosed with Lynch syndrome-associated CRC, about 23 would be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Surveillance in Lynch syndrome populations for ovarian cancer has not been demonstrated to be successful at improving survival.[73]

Section Summary: Lynch Syndrome and Colorectal Cancer Genetic Testing
Direct evidence of clinical utility for genetic testing for Lynch syndrome is not available. Multiple studies have demonstrated clinical utility in testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of

Lynch syndrome patients. One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed and did not follow recommended colonic surveillance. A positive genetic test for an MMR gene variant can also lead to changes in the management of other Lynch syndrome malignancies.

Genetic Testing for Juvenile Polyposis Syndrome and Peutz-Jeghers Syndrome

Clinical Context and Test Purpose

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

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

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

Populations

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

Interventions

The relevant intervention is genetic testing for *SMAD4* and *BMPR1* (for JPS) and *STK11* (for PJS). Commercial testing is available from numerous companies.

Comparators

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

Outcomes

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

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

Genetic testing for *SMAD4* and *BMPR1* (for JPS) and *STK11* (for PJS) may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual of having or developing JPS and PJS.

Study Selection Criteria

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

- Reported on the diagnostic yield of the test.

Clinically Valid

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

Review of Evidence

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

Table 1. Summary of Clinical Validity Studies Assessing Genetic Testing for JPS and PJS

Study	Study Design and Population	Results
Calva-Cerqueira et al (2009)[74]	Observational; 102 unrelated JPS probands analyzed all of whom met clinical criteria for JPS	*SMAD4* and *BMPR1A* variants detected in 41% (42/102) JPS probands
Aretz et al (2007)[75]	Observational; 80 unrelated patients (65 met clinical criteria for typical JPS; 15 presumed to have JPS) were examined by direct sequencing for *SMAD4*, *BMPR1A*, and *PTEN* variants	*SMAD4* and *BMPR1A* variants detected in 60% of typical JPS patients and none in presumed JPS patients; overall diagnostic yield, 49%
Volikos et al (2006)[76]	Observational; 76 clinically diagnosed with PJS	Detection rate of germline variants was about 80% (59/76)
Aretz et al (2005)[77]	Observational; 71 patients (56 met clinical criteria for PJS; 12 presumed to have PJS)	*STK11* variant detected in 52% (37/71)

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

Clinical Useful

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

Direct Evidence

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

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

Chain of Evidence

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

Genetic testing of patients with suspected JPS and PJS has clinical utility:

- To make decisions about a preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis, segmental colectomy).

Genetic testing of individuals who are at-risk relatives of patients suspected of or diagnosed with JPS or PJS has clinical utility:

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

A systematic review of 20 cohort studies with a total of 1644 patients with PJS was published by Lier et al (2010).[32] A total of 349 patients developed 384 malignancies at an average age of 42 years. The lifetime risk for any cancer varied between 37% and 93% with relative risks (RRs) ranging from 9.9 to 18 versus the general population.

Section Summary: Genetic Testing for Juvenile Polyposis Syndrome and Peutz-Jeghers Syndrome

The likelihood of detecting a pathogenic variant is highly dependent on the presence of clinical features and family history. Detection rates have been reported to be between 60% and 41% for JPS, and 52% and 80% for PJS. Direct evidence of the clinical utility for genetic testing of JPS or PJS is not

available. Genetic testing of patients with suspected JPS or PJS or individuals who are at-risk relatives of patients suspected of or diagnosed with a polyposis syndrome or PJS may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from an intensified screening program resulting in psychological relief, and improving health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy.

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.

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

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 U.S. professional society, an international society with U.S. 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)."

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*** **(e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1).**
- Full germline genetic testing ***for Lynch syndrome*** should include DNA sequencing and large rearrangement analysis.
- Patients with multiple colorectal adenomas should be considered for full germline genetic testing of *APC* and/or *MUTYH*.
- Germline testing of *MUTYH* can be initiated by screening for the most common mutations (*G396D, Y179C*) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. ***For nonwhite individuals, full sequencing of*** MUTYH ***should be considered.***"

National Comprehensive Cancer Network

The NCCN guidelines on genetic/familial high-risk assessment of colorectal cancer syndromes (v1.2025, v2.2023) are summarized in Table 2.[80]

Table 2. 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 • ≥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 (i.e., $PREMM_5$, 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: immunohistochemistry; LS: Lynch syndrome; MGPT: multi-gene panel testing; MMR: mismatch repair; MSI: microsatellite instability; NGS: next generation sequencing; PCR: polymerase chain reaction.

[a] LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, 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 3 and 4.[80]

Table 3. 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

Site	Lifetime Risk, %	Screening Procedure and Interval	Approximate Initiation Age, 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.

Table 4. 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 (i.e., anemia) cannot be controlled endoscopically or prevent optimal surveillance for cancer, consideration should be given to gastrectomy and/or colectomy.
[b] While SMAD4 pathogenic variant carriers often have severe upper gastrointestinal tract involvement, 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 (i.e., clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. The Centers for Medicare & Medicaid Services recognizes Lynch syndrome as "an autosomal dominant syndrome that accounts for about 3% to 5% of colorectal cancer cases. [Lynch] syndrome variants occur in the following genes: *hMLH1*, *hMSH2*, *hMSH6*, *PMS2*, and *EPCAM*." The Centers for Medicare & Medicaid Services also recognize familial adenomatous polyposis and *MUTYH*-associated polyposis syndromes and their associated variants.

Ongoing and Unpublished Clinical Trials

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

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02494791	Universal Screening for Lynch Syndrome in Women With Endometrial and Non-Serous Ovarian Cancer	886	July 2025 (status unknown)
NCT04494945	Approaches to Identify and Care for Individuals With Inherited Cancer Syndromes	27500	Jun 2030
NCT06582914	Lynch Syndrome Integrative Epidemiology and Genetics (LINEAGE)	5000	Dec 2054
NCT06501417	EC_ItaLynch: Incorporating Lynch Syndrome Genetic Testing in Standard Medical Care of Patients With Endometrial Cancer (Mainstreaming)	600	Dec 2028
NCT06772844	DNA Methylation Analysis in Stool Samples for Screening of LynchSyndrome-Associated Colorectal Cancer	400	Dec 2028
NCT06863038	Predictive Value of the PREMM5, MMRpredict Models, and the Universal Tumor Screening Strategy for Lynch Syndrome in Vietnam	572	Nov 2027
NCT06989814	Smart Measurement of Circulating Tumor DNA: a Tumor-agnostic Computational Tool to Improve Colorectal Cancer Care	50	Feb 2027

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

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

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

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

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
	0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (*APC*, CDH1, CHEK2, *MLH1*, *MSH2*, *MSH6*, MUTYH, *PMS2*, PTEN, and TP53) (List separately in addition to code for primary procedure)
	0157U	*APC* (*APC* regulator of WNT signaling pathway) (e.g., familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0158U	*MLH1* (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0159U	*MSH2* (mutS homolog 2) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)

Type	Code	Description
	0160U	*MSH6* (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0161U	*PMS2* (PMS1 homolog 2, mismatch repair system component) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (*MLH1, MSH2, MSH6, PMS2*) (List separately in addition to code for primary procedure)
	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81201	*APC* (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	*APC* (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81203	*APC* (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
	81288	*MLH1* (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81292	*MLH1* (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	*MLH1* (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81294	*MLH1* (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81295	*MSH2* (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81296	*MSH2* (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81297	*MSH2* (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81298	*MSH6* (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	*MSH6* (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81300	*MSH6* (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

Type	Code	Description
	81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
	81317	*PMS2* (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	*PMS2* (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81319	*PMS2* (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81403	Molecular Pathology Procedure Level 4
	81435	Hereditary colon cancer-related disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
HCPCS	None	

Policy History

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

Effective Date	Action
02/01/2026	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status
In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to

evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

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

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.