Medical Policy

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Title: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

See also:
- *KRAS, NRAS, BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer*

Professional
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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are suspected of attenuated FAP, MAP, and Lynch syndrome, or are at-risk relatives of patients with FAP	Interventions of interest are: • Genetic testing for *APC*	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are suspected of attenuated FAP, MAP, and Lynch syndrome	Interventions of interest are: • Genetic testing for *MUTYH* after a negative *APC* test result	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are suspected of attenuated FAP, MAP, and Lynch syndrome; CRC; or endometrial cancer and first-degree relative with Lynch	Interventions of interest are: • Genetic testing for MMR genes	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are at-risk relatives of patients with Lynch or family history meeting appropriate criteria, but do not have CRC	Interventions of interest are: • Genetic testing for MMR genes	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who warrant Lynch testing, screen negative on MMR testing, but positive for MSI and lack MSH2 protein expression	Interventions of interest are: • Genetic testing for *EPCAM* variants	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • With CRC in whom MLH1 protein is not expressed on immunohistochemical analysis	Interventions of interest are: • Genetic testing for *BRAF* V600E or *MLH1* promoter methylation	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are suspected of juvenile polyposis syndrome or are at-risk relatives of patients suspected of or diagnosed with JPS	Interventions of interest are: • Genetic testing for SMAD4 and BMPR1A genes	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are suspected of Peutz-Jeghers syndrome or are at-risk relatives of patients suspected of or diagnosed with PJS	Interventions of interest are: • Genetic testing for STK11 gene	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

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).

Objective

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

Background

Hereditary Colorectal Cancers

Currently, 2 types of hereditary 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

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

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

A subset of FAP patients may have an attenuated form of FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP. In the attenuated form of FAP, CRC occurs later in life (at an average age of 50 to 55 years) but lifetime risk of CRC remains high (»70% by age 80 years). The risk of extraintestinal cancer is also lower but cumulative lifetime risk remains high (»38%) compared with the general population.[3,] Only 30% or fewer of attenuated FAP patients have *APC* variants; some of these patients have variants in the *MUTYH* (formerly *MYH*) gene, and this form of the condition is called *MUTYH*-associated polyposis (MAP). MAP occurs with a frequency 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.[4,] Thus, inheritance for high-risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (i.e., between 10 and 99) adenomas are present, and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include *APC*, *MUTYH* if *APC* is negative for variants, and screening for variants associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary by syndrome.[5,]

Testing

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

- Patients at high-risk such as those with a family member who tested positive for FAP and have a known *APC* variant.

- Patients undergoing differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. These patients do not meet the clinical diagnostic criteria for classical FAP and have few adenomatous colonic polyps.
- To confirm FAP in patients with colon cancer with a clinical picture or family history consistent with classical FAP.

Lynch Syndrome

Lynch syndrome is an inherited disorder that results in a higher predisposition to CRC and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3% to 5% of all CRC. People with Lynch syndrome have a 70% to 80% lifetime risk of developing any type of cancer.[6,7,] However the risk varies by genotype. It occurs as a result of germline variant in the mismatch repair (MMR) genes that include *MLH1, MSH2, MSH6*, and *PMS2*. In approximately 80% of cases, the variants are located in the *MLH1* and *MSH2* genes, while 10% to 12% of variants are located in the *MSH6* gene and 2% to 3% in the *PMS2* gene. 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

Testing approach to identify patients with Lynch syndrome is summarized next. 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). MSI detection in 2 of these markers is considered a positive result or "high probability of MSI."[8,]

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

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

Both MSI and IHC have a 5% to 10% false-negative rate. MSI testing performance depends on the specific MMR variant. MSI screening has a sensitivity of about 89% for *MLH1* and *MSH2* and 77% for *MSH6* and a specificity of about 90% for each. The specificity of MSI testing is low because approximately 10% of sporadic CRCs are MSI-positive due to 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.[9,10,] IHC screening has sensitivity for *MLH1*, *MSH2*, and *MSH6* of about 83% and a specificity of about 90% for each.

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

Genetic testing for 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.[11,] 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.[12,]

Novel deletions have been reported to affect the expression of the *MSH2* gene in the absence of an *MSH2* gene variant, and thereby cause Lynch syndrome. In these cases, deletions in *EPCAM*, the gene for the epithelial cell adhesion molecule, are responsible. *EPCAM* testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high and/or IHC shows a lack of *MSH2* expression, but no *MSH2* variant is found by sequencing. *EPCAM* is found just upstream, in a transcriptional sense, of *MSH2*. Deletions of *EPCAM* that encompass the last 2 exons of the *EPCAM* gene, including the polyadenylation signal that normally ends transcription of DNA into messenger RNA, results in transcriptional "read-through" and subsequent hypermethylation of the nearby and downstream *MSH2* promoter. This hypermethylation prevents normal MSH2 protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an *MSH2* variant prevents *MSH2* gene expression.[13,]

Distinct from patients with *EPCAM* deletions, rare cases of Lynch syndrome have been reported without detectable germline MMR variants, although IHC testing demonstrated a loss of expression of one of the MMR proteins. In at least some of these cases, research has identified germline "epivariants," i.e., methylation of promoter regions that control the expression of the MMR genes.[13,14,15,] 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[1,] (low sensitivity but high specificity), Revised Bethesda guidelines[2,] (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 vs attenuated FAP vs MAP.
- For Lynch syndrome patients, genetic testing of the proband with CRC likely benefits the proband where Lynch syndrome is identified, and appropriate surveillance for associated malignancies can be initiated and maintained and benefits family members by identifying the family variant.

Juvenile Polyposis Syndrome
Juvenile polyposis syndrome (JPS) is an autosomal dominant genetic disorder characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract. It is rare, with an estimated incidence of 1 in 100000 to 160000. 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,] JPS 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 one of the following: at least 3 to 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

PJS is also an autosomal dominant genetic disorder, similar to JPS, and characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and nongastrointestinal cancers. It is rare, with an estimated incidence of 1 in 8000 to 200000. 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 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%-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.

REGULATORY STATUS

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

POLICY

A. MMR Gene Testing

1. Genetic testing for MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) may be considered **medically necessary** in the following patients:
   a) Patients with colorectal cancer (CRC), for the diagnosis of Lynch syndrome (see Policy Guidelines).
   b) Patients with endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer (see Policy Guidelines), for the diagnosis of Lynch syndrome.
   c) At-risk relatives (see Policy Guidelines) of patients with Lynch syndrome with a known MMR gene variant.
   d) Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. Whether testing begins with *APC* variants or screening for MMR genes depends on clinical presentation.
   e) Patients without CRC but with a family history meeting the Amsterdam 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.

B. APC Testing

1. Genetic testing for adenosis polyposis coli (*APC*) may be considered **medically necessary** in the following patients:
   a) At-risk relatives (see Policy Guidelines) of patients with familial adenomatous polyposis (FAP) and/or a known *APC* variant.
   b) Patients with a differential diagnosis of attenuated FAP vs *MUTYH*-associated polyposis (MAP) vs Lynch syndrome. Whether testing begins with *APC* variants or screening for mismatch repair (MMR) variants depends on clinical presentation.
2. Genetic testing for *APC* gene variants is **not medically necessary** for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

C. *MUTYH* Testing

1. Genetic Testing for *MUTYH* gene variants may be considered **medically necessary** in the following patients:
   a) Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome and a negative result for *APC* gene variants. A family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

D. *EPCAM* Testing

1. Genetic testing for *EPCAM* gene variants may be considered **medically necessary** when any one of the following 3 major criteria (solid bullets) is met:
   a) Patients with CRC, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when:
      i. Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for a *MSH2* germline variant; **OR**

ii. Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in *MLH1*, *MSH2*, *MSH6*, and *PMS2*; **OR**

b) At-risk relatives (see Policy Guidelines section) of patients with Lynch syndrome with a known *EPCAM* variant; **OR**

c) Patients without CRC but with a family history meeting the Amsterdam 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.

E. *BRAF* V600E OR *MLH1* PROMOTER METHYLATION

1. 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.

F. *SMAD4* AND *BMPR1A* TESTING

1. Genetic testing for *SMAD4* and *BMPR1A* gene variants may be considered **medically necessary** when any one of the following major criteria is met:
   A) Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one 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 a patient suspected of or diagnosed with juvenile polyposis syndrome.

G. *STK11* Testing

1. Genetic testing for *STK11* gene variants may be considered **medically necessary** when any one of the following major criteria is met:
   A.) Patients 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 a patient suspected of or diagnosed with Peutz-Jeghers syndrome.

H. Genetic testing for all other gene variants for Lynch syndrome or CRC is considered **experimental / investigational**.

Policy Guidelines

A. Testing At-Risk Relatives

Due to the high lifetime risk of cancer of the most genetic syndromes discussed in this policy, "at-risk relatives" primarily refers to first-degree relatives. However, some judgment must be allowed, for example, in the case of a small family pedigree, when extended family members may need to be included in the testing strategy. A family history might include at least 2 second-degree relatives with a Lynch syndrome-related cancer, including at least 1 diagnosed before 50 years of age, or at least 3 second-degree relatives with a Lynch syndrome-related cancer, regardless of age.

B. Targeted Familial Variant Testing
It is recommended that, when possible, initial genetic testing for ~~FAP~~ familial adenomatous polyposis or Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the variant found in the affected family member.

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

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

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

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

1) 3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis);
2) 1 should be a first-degree relative of the other 2;
3) 2 or more successive generations affected;
4) 1 or more relatives diagnosed before the age of 50 years;
5) Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma;
6) Tumors should be verified by pathologic examination.
7) Modifications:
    i. EITHER: very small families, which cannot be further expanded, can be considered to have HNPCC with only 2 colorectal cancers in first-degree relatives if at least 2 generations have the cancer and at least 1 case of colorectal cancer was diagnosed by the age of 55 years; **OR**

ii. in families with 2 first-degree relatives affected by colorectal cancer, 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]). The Bethesda guidelines are also considered more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

a. Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old;
b. Presence of synchronous (at the same time) or metachronous (at another time, i.e., a recurrence of) CRC or other HNPCC*–associated tumors, regardless of age;
c. CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old;
d. CRC diagnosed in 1 or more first-degree relatives with a Lynch syndrome-associated tumor, with one of the cancers being diagnosed before 50 years of age;
e. 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.

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

Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are available such MMRpro, PREMM5 (Kastrinos et al [2017]), or MMRpredict. National Comprehensive Cancer Network guidelines recommend (category 2A) testing for Lynch syndrome in individuals with a 5% or higher predicted risk of the syndrome on these risk prediction models.

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

RATIONALE

This evidence review has been regularly updated with searches of the PubMed database. The most recent literature review was performed through July 31, 2020.

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 FAP and MAP is to

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

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing for FAP has clinical validity?; and (2) Does genetic testing for attenuated FAP change patient management in a way that improves outcomes as a result of genetic testing?

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

Patients

The relevant populations of interest is at-risk relatives of patients with FAP and/or a known *APC* variant or those who require a differential diagnosis of attenuated FAP vs MAP vs 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 of 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.
-

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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 on the family history.[47,] Detection rates are higher in classic polyposis (88%) than in nonclassical FAPs such as attenuated colonic phenotypes (57%) or MAP (33%).

Section Summary: Clinically Valid
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%).

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 vs MAP vs 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 ten 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: Clinically Useful
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 vs MAP vs Lynch syndrome may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy.

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 patients diagnosed with CRC or endometrial cancer
- Identify at-risk relatives of patients 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 vs MAP vs Lynch syndrome.

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing for Lynch syndrome has clinical validity?; and (2) Does genetic testing for Lynch syndrome change patient management in a way that improves outcomes as a result of genetic testing?

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

Patients

The relevant populations of interest are patients 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 vs MAP vs 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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

MMR Genes
Microsatellite instability (MSI) and immunohistochemical (IHC) screening tests for MMR variants have similar sensitivity and specificity. MSI 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),[11,] 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.

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 co-segregation of these *EPCAM* variants with Lynch-like disease in families.[13,50,51,52,53,54,] 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%); mean age at diagnosis was 43 years.[55,] 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<0.001).

BRAF V600 or MLH1 Promoter Methylation
Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients.[56,] MLH1 and PMS2 protein stains were absent in 65 patients who were subsequently tested for *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.[57,] 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.[58,]

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 prompt release from an intensified screening program, thereby reducing an emotional burden.

Genetic testing of patients requiring a differential diagnosis of attenuated FAP vs MAP vs 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.[59,60,61,62,63,64,65,] 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 vs 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.[66,]
        - 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.[12,] 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 to segmental resection.[67,] 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.[68,] 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.[69,] 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.[70,] 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.[71,]

Section Summary: Clinically Useful

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 JPS and PJS is:

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

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing for patients suspected of JPS and PJS has clinical validity?; and (2) Does genetic testing for JPS and PJS change patient management in a way that improves outcomes as a result of genetic testing?

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

Patients

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

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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)[72,]	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)[73,]	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)[74,]	Observational; 76 clinically diagnosed with PJS	Detection rate of germline variants was about 80% (59/76)
Aretz et al (2005)[75,]	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.

Section Summary: Clinically Valid
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.

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 prompt release from an intensified screening program, thereby reducing an emotional burden.

A systematic review of 20 cohort study 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 average age of 42 y. Lifetime risk for any cancer varied between 37% and 93% with RRs ranging from 9.9 to 18 vs the general population.

Section Summary: Clinically Useful
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 intensified screening program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy.

Summary of Evidence
For individuals who are suspected of attenuated FAP, MAP, and Lynch syndrome who receive genetic testing for *APC*, or are at-risk relatives of patients with FAP who receive genetic testing for *MUTYH* after a negative *APC* test result, the evidence includes a TEC Assessment. 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 a meaningful improvement in the net health outcome.

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

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

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

For individuals who (1) are suspected of JPS or PJS or (2) are at-risk relatives of patients suspected of or diagnosed with JPS or PJS who receive genetic testing for *SMAD4*, *BMPR1A*, or *STK11* genes, respectively, the evidence includes multiple observational studies. 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 program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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

National Comprehensive Cancer Network

The NCCN guidelines on high-risk colorectal cancer syndromes (v.1.2020) are summarized in Table 2.[76,]

Table 2. Criteria for Evaluation of Lynch Syndrome

Criteria for the Evaluation of Lynch Syndrome
Known LS variant in the family
An individual with colorectal or endometrial cancer and any of the following: • Diagnosed <50 y • Another synchronous or metachronous LS-related cancer[a] • 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
An individual with colorectal or endometrial cancer at any age with tumor showing evidence of MMR deficiency, either by MSI or loss of MMR protein expression[b]
Family history of any of the following:

Criteria for the Evaluation of Lynch Syndrome
• ≥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 an LS-related cancer[a] or unaffected individual with ≥5% risk of having an MMR gene variant based on predictive models (PREMM5, MMRpro, MMRpredict)
An individual with a colorectal tumor with MSI-high histology (i.e., presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) diagnosed ≤60 y

LS: Lynch syndrome; MMR: mismatch repair; MSI: microsatellite instability.

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

[b] Tumor screening for MMR deficiency is appropriate for all colorectal and endometrial cancers regardless of age at diagnosis, however, germline genetic testing is generally reserved for patients with early age at diagnosis; positive family history; or abnormal tumor testing results; MSI or loss of MMR protein expression.

[c] There are recent data that resulted in a lower threshold of ≥2.5% for the PREMM5 predictive model risk for having an MMR gene variant. 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. It is not known how this applies to the general population of unaffected individuals.

Additionally, the NCCN guidelines (v.2.2020) recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years.[27,76,] Genetic testing is recommended for at-risk family members of patients with positive variants in *MLH1*, *MSH2*, *MSH6*, and *PMS2*. The NCCN guidelines also indicate *BRAF* V600E testing or *MLH1* promoter methylation testing may be used when *MLH1* is not expressed in the tumor on immunohistochemical analysis to exclude a diagnosis of Lynch syndrome. 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.

The NCCN guidelines for colon cancer (v.4.2020)[26,]and for CRC screening v.2.2020)[77,] recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year post surgery and, if normal, again in 3 years, then every 5 years based on findings. However, because of the high likelihood of cancer, colonoscopy is recommended every one to two years throughout life for patients with Lynch syndrome before cancer diagnosis; and the high likelihood of a second primary cancer is based on a first cancer diagnosis.[78,] The NCCN guidelines on genetic/familial high-risk assessment for colorectal 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."[76,] "MSH6 variant carriers should begin surveillance with colonoscopy at age 30 to 35 years, and PMS2 carriers should begin surveillance at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on the ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 years for MSH6 and PMS2 variant carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years."

The NCCN guidelines for colon cancer (v.4.2020) recommend that all newly diagnosed patients with colon cancer be tested for mismatch repair (MMR) or microsatellite instability (MSI)..[26,] The NCCN guidelines for uterine neoplasm (v.2.2020) also recommend universal screening for MMR genes.[27,]

There are limited data on the efficacy of various screening modalities in juvenile polyposis syndrome and Peutz-Jeghers syndrome. The NCCN cancer risk and surveillance 2 category 2A recommendations for these indications are summarized in Tables 3 and 4.[76,]

Table 3. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome

Site	Lifetime Risk, %	Screening Procedure and Interval	Initiation Age, y
Breast	32 -54	• Mammogram and breast MRI annually • Clinical breast exam every 6 mo	»30 y
Colon	39	Colonoscopy every 2-3 y	Late teens
Stomach	29	Upper endoscopy every 2-3 y	Late teens
Small intestine	13	Small bowel visualization (CT or MRI enterography or video capsule endoscopy baseline at 8-10 y with follow-up interval based on findings but at least by age 18, then every 2-3 y, though this may be individualized, or with symptoms)	»8 to 10 y
Pancreas	11-36	Magnetic resonance cholangiopancreatography with contrast or endoscopic ultrasound every 1-2 h	»30 to 35 y
Ovary(typically benign sex cord/Sertoli cell tumors)Cervix (typically cervical adenoma malignum)Uterus	18-21 10 9	• Pelvic examination and Pap smear annually • Consider transvaginal ultrasound	»18 to 20 y
Testes (typically sex cord/Sertoli cell tumors)	9	Annual testicular exam and observation for feminizing changes	»10 y
Lung	7 -17	• Provide education about symptoms and smoking cessation • No other specific recommendations have been made	

CT: computed tomography; MRI: magnetic resonance imaging.

Table 4. Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome

Site	Lifetime Risk, %	Screening Procedure and Interval	Initiation Age, y
Colon	40-50	Colonoscopy: Repeat every 2-3 years. If polyps are found repeat at shorter intervals based on polyp size, number, and pathology.[a]	»15 y

Site	Lifetime Risk, %	Screening Procedure and Interval	Initiation Age, y
Stomach	21 if multiple polyps	Upper endoscopy: Repeat every 2-3 years. If polyps are found repeat at shorter intervals based on polyp size, number, and pathology.[a]	»15 y
Small intestine	Rare, undefined	No recommendations made	
Pancreas	Rare, undefined	No recommendations made	
HHT	Undefined	In individuals with *SMAD4* variants, screen for vascular lesions associated with HHT	Within first 6 mo of age

HHT: hereditary hemorrhagic telangiectasia.
[a] In families where a SMAD4 or BMPR1A mutation is not identified, consider extending colonoscopy/upper endoscopy intervals in at-risk individuals who have no polyps from 2-3 years to 5 years beginning at age 20, and then every 10 years beginning at age 40s,

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

For Lynch syndrome, the College recommended:
"All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency.

Analysis may be done by immunohistochemical testing for the *MLH1/MSH2/MSH6/PMS2* proteins and/or testing for microsatellite instability. Tumors that demonstrate loss of *MLH1* should undergo BRAF testing or analysis for *MLH1* promoter hypermethylation.

Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF variant or hypermethylation of *MLH1*), a known family variant associated with LS [Lynch syndrome], or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.[79,]

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

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

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

For juvenile polyposis syndrome, the College recommended:
"Genetic evaluation of a patient with possible JPS [juvenile polyposis syndrome] should include testing for *SMAD4* and *BMPR1A* mutations"

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

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

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

For Peutz-Jeghers syndrome, the College recommended:
"Genetic evaluation of a patient with possible PJS [Peutz-Jeghers syndrome] should include testing for *STK11* mutations."

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

American Society of Clinical Oncology and Society of Surgical Oncology
The American Society of Clinical Oncology (2015) concluded the European Society for Medical Oncology clinical guidelines published in 2013 were based on the most relevant scientific evidence and therefore endorsed them with minor qualifying statements (in bold italics).[80,] The recommendations as related to genetic testing hereditary CRC syndromes are summarized below:

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

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.

Ongoing and Unpublished Clinical Trials
Some currently 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
NCT04494945	Approaches to Identify and Care for Individuals With Inherited Cancer Syndromes	27500	Jun 2030
Unpublished			
NCT01850654	Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome	4000	Jan 2018 (completed)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

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 (rB-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 variant
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication / deletion variant
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
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 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex pcr in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) ang (angiogeni
81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11 [Note: some of genes discussed in the policy are included in this panel
81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11 [Note: some of the genes discussed in the policy are included in this panel]
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) , (new eff 10/01/2019- panel including many genes discussed in this policy;
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)
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

ICD-10 Diagnoses

C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
D12.0	Benign neoplasm of cecum
D12.1	Benign neoplasm of appendix
D12.2	Benign neoplasm of ascending colon
D12.3	Benign neoplasm of transverse colon
D12.4	Benign neoplasm of descending colon
D12.5	Benign neoplasm of sigmoid colon
D12.6	Benign neoplasm of colon, unspecified
D12.7	Benign neoplasm of rectosigmoid junction
D12.8	Benign neoplasm of rectum
D12.9	Benign neoplasm of anus and anal canal
D01.0	Carcinoma in situ of colon
D01.1	Carcinoma in situ of rectosigmoid junction
D01.2	Carcinoma in situ of rectum
D01.3	Carcinoma In Situ Of Anus And Anal Canal
D01.40	Carcinoma In Situ Of Unspecified Part Of Intestine
D01.5	Carcinoma In Situ Of Liver, Gallbladder And Bile Ducts
D01.6	Carcinoma in situ of other and unspecified digestive organs; code range
D01.7	Carcinoma In Situ Of Other Specified Digestive Organs
D01.9	Carcinoma In Situ Of Digestive Organ, Unspecified
Q85.8	Other phakomatoses, not elsewhere classified (includes Puetz-Jeghers Syndrome
Z80.0	Family history of malignant neoplasm of digestive organs
Z31.5	Encounter for genetic counseling
Z85.030	Personal History Of Malignant Carcinoid Tumor Of Large Intestine
Z85.038	Personal History Of Other Malignant Neoplasm Of Large Intestine
Z85.040	Personal History Of Malignant Carcinoid Tumor Of Rectum
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus

REVISIONS

05-13-2011	Policy added to the bcbsks.com web site.
01-01-2012	In the Coding section: ▪ Added the new codes: 81210, 81292-81301
04-10-2012	In the Coding section: ▪ Replaced Diagnosis code 183.1 with correct code 183.2. ▪ Removed HCPCS codes: S3828, S3829, S3830, S3831 (Deleted codes, effective April 1, 2012.)

01-15-2013	In the Coding section: ▪ Added CPT codes: 81401, 81406 ▪ Added new CPT codes: 81201, 81202, 81203(Effective 01-01-2013) ▪ Removed CPT codes:83890, 83892, 83898, 83902, 83904, 83905, 83906, 83912 (Effective 12-31-2012)
03-26-2013	Updated Description section.
	In Policy section: ▪ In Item I, Note, Amsterdam II Criteria, added "6. Modifications: EITHER: very small families, which cannot be further expanded, can be considered to have HNPCC with only 2 colorectal cancers in first-degree relatives if at least two generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years; OR: in families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient." ▪ In Item I, Note, Revised Bethesda Criteria, added "6. Colorectal cancer diagnosed with one or more first-degree relatives with HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous bland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed under age 50 years, OR colorectal cancer diagnosed in two or more first-or second-degree relatives with HNPCC related tumor, regardless of age. (15)"
	Updated Rationale section.
	Updated Reference section.
08-21-2013	In Coding section: ▪ Removed CPT code 81210. ▪ Added ICD-10 Diagnosis codes *(Effective October 1, 2014)*
01-01-2015	Policy posted 01-16-2015
	In Coding section: ▪ Added CPT Code: 81288 (Effective January 1, 2015)
03-18-2015	In Title section: ▪ Changed title name from "Genetic Testing for Inherited Susceptibility to Colon Cancer, Including Microsatellite Instability Testing"
	Updated Description section.
	In Policy section: ▪ Removed Amsterdam II criteria and Revised Bethesda guidelines. ▪ In Policy Guidelines, added items 6-9.
	Updated Rationale section.
	In Coding section: ▪ Added CPT Codes 81210, 81317, 81318, 81319, and 81403. ▪ Removed CPT Code 81406.
	Updated References section.
01-01-2016	In Coding section: ▪ Revised nomenclature to CPT codes: 81210 and 81401.
02-03-2016	Updated Description section.
	In Policy section: ▪ Added statement on genetic counseling to Policy Guidelines.
	Updated Rationale section.
	Updated References section.
	Added Appendix section.
05-25-2016	Updated Description section.

	In Policy section: ▪ Revised Policy Guideline Item 6.
	Updated Rationale section.
	Updated References section.
11-09-2016	In Policy section: ▪ In Item I B, removed "when feasible" and "who meet the revised Bethesda criteria (see Policy Guidelines below)" and added "or immunohistochemical (IHC) analysis of tumors" and "or endometrial" to read, "Microsatellite instability (MSI) testing or immunohistochemical (IHC) analysis of tumors may be considered medically necessary as an initial test in persons with colorectal or endometrial cancer in order to identify those persons who should proceed with HNPCC variant analysis."
	In Coding section: ▪ Added CPT codes: 88341, 88342, 88344.
12-08-2017	Updated Description section.
	In Policy section: ▪ Added new Item I B, "HNPCC genetic testing is considered experimental / investigational for all other indications." ▪ Previous Item I B is now Item I C. ▪ Added new Item I D, "MSI testing or IHC analysis of tumors is considered experimental / investigational for all other indications." ▪ Added new Item II B, "APC genetic testing is considered experimental / investigational for all other indications." ▪ Previous Item II B is now Item II C. ▪ Added new Item II D, "MAP genetic testing is considered experimental / investigational for all other indications."
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
02-18-2019	Updated Description section.
	In Policy section: ▪ Removed the previous policy language: "I. Lynch syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer [HNPCC]): A. Genetic testing for HNPCC (MLH1, MSH2, MSH6, PMS2 sequence analysis) is considered medically necessary when one of the following criteria are met: 1. Meets Amsterdam II criteria or revised Bethesda guidelines (see Policy Guidelines below); or 2. A first-* or second-degree** relative with an HNPCC variant (genes MLH1, MSH2, MSH6, PMS2); or 3. Endometrial cancer 50 years of age or younger. B. HNPCC genetic testing is considered experimental / investigational for all other indications. C. Microsatellite instability (MSI) testing or immunohistochemical (IHC) analysis of tumors may be considered medically necessary as an initial test in persons with colorectal or endometrial cancer in order to identify those persons who should proceed with HNPCC variant analysis. D. MSI testing or IHC analysis of tumors is considered experimental / investigational for all other indications. II. Familial Adenomatous Polyposis and associated variance: A. Adenosis polyposis coli (APC) genetic testing is considered medically necessary for either of the following indications: 1. Greater than 10 colonic polyps; or 2. First-degree* relatives diagnosed with familial adenomatous polyposis (FAP) or with a documented APC variant. The specific APC variant should be identified in the affected first-degree relative with FAP prior to testing the member, if feasible. Full sequence APC genetic testing is considered medically necessary only when it is not possible to determine the family variant first. B. APC genetic testing is considered experimental / investigational for all other indications. C. Testing for MYH variants is considered medically necessary for any of the following indications: 1. Personal history of 10 to 20 adenomatous

	polyposis who have negative APC variant testing and a negative family history for adenomatous polyposis; OR 2. Personal history of 10 to 20 adenomatous polyposis whose family history is consistent with recessive inheritance (i.e., family history is positive only for sibling[s]); OR 3. Asymptomatic siblings of individuals with known MYH polyposis. D. MAP genetic testing is considered experimental / investigational for all other indications. *First-degree relatives are parents, siblings, and offspring. ** Second-degree relatives are aunts, uncles, grandparents, niece, nephews or half-siblings. ⅄Hereditary nonpolyposis colorectal cancer (HNPCC)-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome." ▪ Added new policy language, "A. MMR Gene Testing 1. Genetic testing for MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) may be considered medically necessary in the following patients: a) Patients with colorectal cancer (CRC), for the diagnosis of Lynch syndrome (see Policy Guidelines. b) Patients with endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer (see Policy Guidelines), for the diagnosis of Lynch syndrome. c) At-risk relatives (see Policy Guidelines) of patients with Lynch syndrome with a known MMR gene variant. d) Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. Whether testing begins with *APC* variants or screening for MMR genes depends on clinical presentation. e) Patients without CRC but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR variants. B. APC Testing 1. Genetic testing for adenosis polyposis coli (*APC*) may be considered medically necessary in the following patients: a) At-risk relatives (see Policy Guidelines) of patients with familial adenomatous polyposis (FAP) and/or a known *APC* variant. b) Patients with a differential diagnosis of attenuated FAP vs *MUTYH*-associated polyposis (MAP) vs Lynch syndrome. Whether testing begins with *APC* variants or screening for mismatch repair (MMR) variants depends on clinical presentation. 2. Genetic testing for *APC* gene variants is not medically necessary for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis. C. *MUTYH* Testing 1. Testing for *MUTYH* gene variants may be considered medically necessary in the following patients: a) Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome and a negative result for *APC* gene variants. A family history of no parents or children with FAP is consistent with MAP (autosomal recessive). D. *EPCAM* Testing 1. Genetic testing for *EPCAM* gene variants may be considered medically necessary when any one of the following 3 major criteria (solid bullets) is met: 1) Patients with CRC, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when: i. Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for a *MSH2* germline variant; OR ii. Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in *MLH1*, *MSH2*, *MSH6*, and *PMS2*; OR b) At-risk relatives (see Policy Guidelines section) of patients with Lynch syndrome with a known *EPCAM* variant; OR c) Patients without CRC but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR variants, and when sequencing for MMR variants is negative. E. *BRAF* V600E or *MLH1* promoter methylation 1. 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. F. *SMAD4* and *BMPR1A* Testing 1. Genetic testing for *SMAD4* and *BMPR1A* gene variants may be considered medically necessary when any one of the following major criteria (solid bullets) is met: a) Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following: i. at least 3 to 5 juvenile polyps in the colon ii.

	multiple juvenile polyps in other parts of the gastrointestinal tract iii. any number of juvenile polyps in a person with a known family history of juvenile polyps. b) At-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome. G. *STK11* Testing 1. Genetic testing for *STK11* gene variants may be considered medically necessary when any one of the following major criteria (solid bullets) is met: a) Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following: i. presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine ii. characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers iii. family history of Peutz-Jeghers syndrome b) At-risk relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome. H. Genetic testing for all other gene variants for Lynch syndrome or CRC is considered experimental / investigational." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Removed CPT codes: 81401, 88341, 88342, 88344. ▪ Updated coding bullets.
	Updated References section.
	Removed Appendix section.
04-24-2019	In Policy section: ▪ In Item A 1 e, removed "or Revised Bethesda" to read, "Patients without CRC but with a family history meeting the Amsterdam criteria, when no affected family members have been tested for MMR variants." ▪ In Item D 1 c, removed "or Revised Bethesda" and "and when sequencing for MMR variants is negative" to read, "Patients without CRC but with a family history meeting the Amsterdam criteria, when no affected family members have been tested for MMR variants."
07-01-2019	In Coding section: ▪ Added new CPT code: 0101U
07-09-2020	Published 07-09-2020. Effective 06-15-2020 Updated Description section Updated Coding section- • Removed: CPT 81403 • Added CPT: 81435, 81436, 0130U • Removed ICD 10: C17.0, C17.1,C17.2, C17.3, C17.8,C17.9, , C25.1, C25.2, C56.1, C56.2, C56.9, C57.00, C579.01, C57.02, C57.10, C57.11, C57.12, C57.3, C5.20, C57.21, C57.22, C60.1, C71.0, C71.1, C71.2, C71.3, C71.4, C71.5, C71.6, C717.7, C71.8, C71.9 • Added ICD 10: D01.3, D01.4, D01.5, D01.6, D01.7, D01.8, D01.9, Q85.8, Z31.5 Updated Rationale section Updated Reference section
05-21-2021	Updated Description section
	In Policy Section: • <u>Added</u> the following: ○ In Item A.1.e and Item D.1.c, "or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model (e.g. MMRpro, PREMM5 or MMRpredict)," ○ In Item C.1, "Genetic" ○ In policy guideline 1, "A family history might include at least 2 second-degree relatives with a Lynch syndrome-related cancer, including at least 1 diagnosed before 50 years of age, or at least 3 second-degree relatives with a Lynch syndrome-related cancer, regardless of age."

	○ In policy guideline C., "* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel. Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are available such MMRpro, PREMM5 (Kastrinos et al [2017]), or MMRpredict. National Comprehensive Cancer Network guidelines recommend (category 2A) testing for Lynch syndrome in individuals with a 5% or higher predicted risk of the syndrome on these risk prediction models." • <u>Replaced</u> the following: ○ In Item F.1.A.1, "3 to" with "5" ○ In Item F.1.A.2, "in other parts of" with "found throughout" ○ In Item G.1.A.1, "small intestine" with "gastrointestinal tract" ○ Policy guideline A, "majority of the" with "most" • <u>Removed</u> the following: ○ In Items F.1 and G.1, "(solid bullets) ○ In policy guidelines removed the genetic nomenclature update section and the following: **A.** Several Clinical Laboratory Improvement Amendments (CLIA)–licensed clinical laboratories offer MMR gene variant testing for Lynch syndrome. For example, the GeneTests website (available online at: http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2622?db) lists 32 U.S.-located laboratories that offer this service. In at least 1 laboratory, Lynch syndrome variant testing is packaged under 1 copyrighted name. The COLARIS® test from Myriad Genetic Laboratories includes sequence analysis of MLH1, MSH2, MSH6, and PMS2; large rearrangement analysis for MLH1, MSH2, PMS2, and MSH6 large deletions/duplications; and analysis for large deletions in the EPCAM gene near MSH2. Note that there may be 2 versions of this test, the COLARIS (excludes PMS2 testing) and COLARIS Update (includes PMS2 testing). Individualized testing (e.g., targeted testing for a family variant) can also be requested. The COLARISPLUS test includes full sequence analysis of MLH1, MSH2, MSH6, PMS2, and MYH genes and rearrangement analysis of MLH1, MSH2, MSH6, MYH, and EPCAM by microarray comparative genomic hybridization analysis, and multiplex ligation-dependent probe amplification analysis for PMS2. **B.** Similarly, GeneTests lists 15 U.S.-based CLIA-licensed clinical laboratories that provide APC variant testing and 14 that provide MUTYH variant testing. The COLARIS® AP test from Myriad Genetic Laboratories includes DNA sequencing analysis of the APC and MUTYH genes, as well as analysis of large rearrangements in the APC gene that are not detected by DNA sequencing.
	Updated Rationale section
	In Coding section: • Added Codes: 0157U, 0158U, 0159U, 0160U, 0161U, 0162U, 0238U • Added ICD-10 diagnosis code Z85.040 • Removed ICD-10 diagnosis code D01.8
	Updated References section

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