Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy #  00190
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Current Effective Date:  11/21/2018

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

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

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

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

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

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

When Services Are Considered Not Medically Necessary
Genetic testing for APC gene variants is not medically necessary for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

MUTYH TESTING
Based on the review of available data, the Company may consider genetic testing for MUTYH gene variants may be considered medically necessary in the following patients:

- 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).

MMR GENE TESTING
Based on the review of available data, the Company may consider genetic testing for mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) in the following patients to be eligible for coverage:
Patients with colorectal cancer (CRC) who meet the revised Bethesda Guidelines, for the diagnosis of Lynch syndrome

Patients with endometrial cancer and 1 first-degree relative diagnosed with a Lynch-associated cancer, for the diagnosis of Lynch syndrome.

At-risk relatives of patients with Lynch syndrome with a known mismatch repair (MMR) gene variant.

Patients with a differential diagnosis of attenuated familial adenomatous polyposis (FAP) vs. MUTYH-associated polyposis (MAP) vs. Lynch syndrome. Whether testing begins with polyposis coli (APC) variants or screening for mismatch repair (MMR) genes depends upon clinical presentation.

Patients without colorectal cancer (CRC) but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for mismatch repair (MMR) variants.

Patients with ≥5% risk of Lynch Syndrome on one of the following mutation prediction models: MMRpro, PREMM1,2,6, or MMRpredict.

EPCAM TESTING
Based on the review of available data, the Company may consider genetic testing for the epithelial cell adhesion molecule (EPCAM) gene variants to be eligible for coverage when any one of the following 3 major criteria are met:

Patients with colorectal cancer (CRC), for the diagnosis of Lynch syndrome when:

- Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for aMSH2 germline variant; OR
- Tumor tissue shows a high level of microsatellite instability (MSI) and patient is negative for a germline variant in MSH2, MLH1, PMS2, and MSH6; OR

At-risk relatives of patients with Lynch syndrome with a known epithelial cell adhesion molecule (EPCAM) variant; OR

Patients without colorectal cancer (CRC) but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for mismatch repair (MMR) variants, and when sequencing for mismatch repair (MMR) variants is negative.

BRAF V600E OR MLH1 PROMOTER METHYLATION
Based on the review of available data, the Company may consider genetic testing for BRAF V600E or MLH1 promoter methylation to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer (CRC) tumor on immunohistochemical (IHC) analysis to be eligible for coverage.
SMAD4 AND BMPR1A TESTING
Based on the review of available data, the Company may consider Genetic testing for SMAD4 and BMPR1A gene variants when any one of the following major criteria (solid bullets) is met to be eligible for coverage:

- Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
  - at least 3 to 5 juvenile polyps in the colon
  - multiple juvenile polyps in other parts of the gastrointestinal tract
  - any number of juvenile polyps in a person with a known family history of juvenile polyps.
- At-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome.

STK11 TESTING
Based on the review of available data, the Company may consider Genetic testing for STK11 gene variants when any one of the following major criteria (solid bullets) is met to be eligible for coverage:

- Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
  - presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine
  - characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - family history of Peutz-Jeghers syndrome
- At-risk relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome.

GENETIC COUNSELING
Based on the review of available data, the Company may consider pre- and post-test genetic counseling as an adjunct to the genetic testing itself to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on the review of available data, the Company may consider genetic testing for all other gene variants for Lynch syndrome or colorectal cancer (CRC) to be investigational.*

Policy Guidelines
TESTING AT-RISK RELATIVES
Due to the high lifetime risk of cancer of most genetic syndromes discussed in this policy, “at-risk relatives” primarily refers to first-degree relatives. However, some judgment must be allowed, eg, in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.
TARGETED FAMILIAL VARIANT TESTING

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

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

EVALUATION FOR LYNCH SYNDROME

For patients with CRC being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test or the IHC test with or without *BRAF* gene variant testing, should be used as an initial evaluation of tumor tissue before MMR gene analysis. Both tests are not necessary. Proceeding to MMR gene sequencing would depend on 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.

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=genetests) 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 (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 are 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 COLARIS® PLUS 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*.

Similarly, GeneTests lists U.S.-based CLIA-licensed clinical laboratories that provide *APC* variant testing and those that provide *MUTYH* variant testing. The COLARIS AP test (Myriad Genetic Laboratories) includes DNA sequencing analysis of the *APC* and *MUTYH* genes, as well as analysis of large rearrangements in the *APC* gene not detected by DNA sequencing.
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):

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

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

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

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, 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.

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

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
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</tbody>
</table>

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

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Background/Overview
HEREDITARY COLORECTAL CANCERS
Currently, 2 types of hereditary colorectal cancers are well-defined: FAP and Lynch syndrome (formerly hereditary nonpolyposis CRC). Lynch syndrome has been implicated in some endometrial cancers as well.

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

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

A subset of FAP patients may have an attenuated form of FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP. In the attenuated form of FAP, CRC occurs later in life (at an average age of 50 to 55 years) but lifetime risk of CRC remains high (≈70% by age 80 years). The risk of extra-intestinal cancer is also lower but cumulative lifetime risk remains high (≈38%) compared with the general population. Only 30% or fewer of attenuated FAP patients have APC variants; some of these patients have variants in the MUTYH (formerly MYH) gene, and this form of the condition is called MAP. MAP occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH variants are associated with a cumulative CRC risk of about 80% by age 70, whereas the monoallelic MUTYH variant–associated risk of CRC appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (ie, between 10 and 99) adenomas are present, and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include APC, MUTYH if APC is negative for variants, and screening for variants associated with Lynch syndrome.

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

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

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

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

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

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

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

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

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

Recently, 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, resulting 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. Several studies have characterized such *EPCAM* deletions, established their correlation with the presence of *EPCAM-MSH2* fusion messenger RNAs (apparently nonfunctional) and with the presence
of MSH2 promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM variants with Lynch-like disease in families.

Distinct from patients with EPCAM deletions, rare cases of Lynch syndrome have been reported without detectable germline MMR variants although IHC testing demonstrated a loss of expression of one of the MMR proteins. In at least some of these cases, research has identified germline "epivariants," i.e., methylation of promoter regions that control the expression of the MMR genes. Such methylation may be isolated or be in conjunction with a linked genetic alteration near the affected MMR gene. The germline epivariants may arise de novo or may be heritable in Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic CRC wherein the tumor tissue may show MLH1 promoter methylation and IHC 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 (low sensitivity but high specificity), Bethesda guidelines (better sensitivity but poorer specificity) and risk prediction models (eg, MMRpro; PREMM5; MMRpredict). While family history is an important risk factor and should not be discounted in counseling families, it has poor sensitivity and specificity for identifying Lynch syndrome. Based on this and other evidence, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing all newly diagnosed patients with CRC for Lynch syndrome, using a screening strategy based on MSI or IHC (with or without BRAF) followed by sequencing in screen-positive patients. This recommendation includes genetic testing for the following types of patients:

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

Juvenile Polyposis Syndrome
Juvenile polyposis syndrome (JPS) is an autosomal dominant genetic disorder characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract. It is rare, with an estimated
incidence of 1 in 100,000 to 160,000. Generalized juvenile polyposis refers to polyps in the upper and lower gastrointestinal tract, and juvenile polyposis coli refers to polyps of the colon and rectum. Those with JPS are at a higher risk for colorectal and gastric cancer. Approximately 60% of patients with JPS have a germline variant in the \textit{BMPR1A} gene or the \textit{SMAD4} gene. Approximately 25% of patients have de novo variants. In most cases, polyps appear in the first decade of life and most patients are symptomatic by age 20 years. Rectal bleeding is the most common presenting symptom, occurring in more than half of patients. Other presenting symptoms include prolapsing polyp, melena, pain, iron deficiency anemia, and diarrhea.

As noted, individuals with JPS are at increased risk for colorectal and gastric cancer. By 35 years of age, the cumulative risk of CRC is 17% to 22%, which increases to 68% by age 60 years. The estimated lifetime risk of gastric cancer is 20% to 30%, with a mean age at diagnosis of 58 years. JPS may also be associated with hereditary hemorrhagic telangiectasia. The most common clinical manifestations of hereditary hemorrhagic telangiectasia are telangiectasias of the skin and buccal mucosa, epistaxis, and iron deficiency anemia from bleeding.

\textbf{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. It is recommended that individuals who meet clinical criteria for JPS undergo genetic testing for a germline variant in the \textit{BMPR1A} and \textit{SMAD4} genes for a confirmatory diagnosis of JPS and to counsel at-risk family members.

\textbf{Peutz-Jeghers Syndrome}

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

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

\textbf{Diagnosis}

A clinical diagnosis of PJS is made if an individual meets two or more of the following criteria: presence two or more histologically confirmed PJ polyps of the small intestine or characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, fingers, or family history of PJS. Individuals who meet...
clinical criteria for PJS should undergo genetic testing for a germline variant in the \textit{STK11} gene for a confirmatory diagnosis of PJS and counseling at-risk family members. In addition, if there is a known \textit{SMAD4} variant in the family, genetic testing should be performed within the first 6 months of life due to hereditary hemorrhagic telangiectasia risk.

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**

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

**Centers for Medicare and Medicaid Services (CMS)**

Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (i.e. clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. The CMS recognizes Lynch syndrome as "an autosomal dominant syndrome that accounts for about 3 to 5\% of CRC cases. [Lynch] syndrome mutations occur in the following genes: hMLH1, hMSH2, hMSH6, PMS2, and EPCAM." CMS also recognizes FAP and MAP syndromes and their associated variants.

**Rationale/Source**

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 \textit{MUTYH}-associated polyposis is to
Identify at-risk relatives of patients with FAP and/or a known 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 FAP change patient management in a way that improves outcomes as a result of genetic testing?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population 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 comparator of interest is no genetic testing.

Outcomes
The potential beneficial outcomes of primary interest would be early detection of 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 -negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Timing
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.

Setting
Ordering and interpreting genetic testing may be complex and is best done by experienced specialists such as gastroenterologists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

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

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- 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 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 informed by a TEC Assessment (1998). The additional information on attenuated FAP and on MAP diagnostic criteria and genetic testing is based on information from GeneReviews and from several publications that build on prior, cited research.

The analytic sensitivity and specificity for APC and MUTYH are both 99%. Clinical sensitivity for classic FAP is about 95%; about 90% of pathogenic variants are detected by sequencing while 8% to 12% of pathogenic variants are detected by deletion and duplication testing. Among Northern European whites, 85% of pathogenic MUTYH variants are detected by the 2 variant test (Y165C, G382D) and 98% of pathogenic MUTYH variants are detected by full gene sequencing.

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. GeneReviews reported that the likelihood of detecting an APC pathogenic variant is highly dependent on the severity of colonic polyposis and on the family history. 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, 85% of pathogenic MUTYH variants are detected by the 2 variant test, and 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 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
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 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) offered the following conclusions:
- Genetic testing for FAP may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.
- At-risk subjects are considered to be those with greater than 10 adenomatous polyps or close relatives of patients with clinically diagnosed FAP or of patients with an identified APC variant.
- The optimal testing strategy is to define the specific genetic variant in an affected family member and then test the unaffected family members to see if they have inherited the same variant.

Table 1 summarizes clinical utility studies assessing genetic testing for FAP.

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.

Table 1. Summary of Clinical Utility Studies for Genetic Testing for FAP

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjork et al (2000)</td>
<td>Observational: 195 confirmed cases of FAP underwent ileorectal anastomosis and followed for, on average, 14 years post-surgery</td>
<td>Cumulative risk of rectal cancer mortality was 7% at 20 years postsurgery and cumulative mortality was</td>
</tr>
</tbody>
</table>

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Järvinen (1992)</td>
<td>Observational: 251 individuals from 81 affected families; 76 individuals diagnosed during family screening vs 116 symptomatic individuals with probands</td>
<td>11.1% at the age of 70 y, indicating a substantial risk of developing cancer even after surgery</td>
</tr>
<tr>
<td>Vasen et al (1990)</td>
<td>Observational: CRC rate compared in 230 confirmed FAP cases; 104 symptomatic and 126 at-risk family members identified by screening</td>
<td>65.5% of symptomatic cases had CRC vs 6.6% cases among those screened during family screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47% of symptomatic cases had CRC at a mean age of 35 y vs 4% at 24 y</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; FAP: familial adenomatous polyposis.

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 CRC GENETIC TESTING

Clinical Context and Test Purpose

The purpose of genetic testing for Lynch syndrome is to:

- Detect Lynch syndrome in patients diagnosed with colorectal or endometrial cancer
- Identify at-risk relatives of patients with a diagnosed Lynch syndrome and/or a known MMR variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria
- 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 PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients diagnosed with colorectal 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 the Amsterdam or Revised Bethesda criteria 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.

Timing
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.

Setting
Ordering and interpreting genetic testing may be complex and is best done by experienced specialists such as gastroenterologists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria
For the evaluation of 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 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).

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), a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009), and an EGAPP recommendation (2009) for genetic testing in CRC. 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.

Moreira et al (2012) compared universal testing of CRC patients with alternative screening approaches. The alternative screening approaches included using the Bethesda guidelines, the Jerusalem recommendations, and a selective strategy including only those diagnosed with CRC before age 70, or after age 70 if meeting the Bethesda guidelines. In the analysis of 10206 newly diagnosed CRC patients from 4 large cohort studies, MSI testing was used in 2150 patients, and immunostaining was used in 2278 patients, while both MSI and immunostaining were used in 5591 patients. MMR gene variants were found in 312 (3.1%) patients overall. The universal screening approach was superior to the other screening approaches in the population-based cohorts (n=3671 probands). Table 2 summarizes the results of the different screening approaches.

### Table 2. Diagnostic Results of the Different Screening Approaches

<table>
<thead>
<tr>
<th>Screening Approach</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
<th>Diagnostic Yield (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal</td>
<td>100 (95 CI, 99.3 to 100)</td>
<td>93 (95 CI, 92.0 to 93.7)</td>
<td>2.2 (95 CI, 1.7 to 2.7)</td>
</tr>
<tr>
<td>Bethesda guidelines</td>
<td>87.8 (95 CI, 78.9 to 93.2)</td>
<td>97.5 (95 CI, 96.9 to 98.0)</td>
<td>2.0 (95 CI, 1.5 to 2.4)</td>
</tr>
<tr>
<td>Jerusalem recommendations</td>
<td>85.4 (95 CI, 77.1 to 93.6)</td>
<td>96.7 (95 CI, 96.0 to 97.2)</td>
<td>1.9 (95 CI, 1.4 to 2.3)</td>
</tr>
<tr>
<td>Selective strategy</td>
<td>95.1 (95 CI, 89.8 to 99.0)</td>
<td>95.5 (95 CI, 94.7 to 96.1)</td>
<td>2.1 (95 CI, 1.6 to 2.6)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

However, the diagnostic yield differences between the screening approaches were small, and the false-positive yield was 2.5% with universal screening. In the selective strategy, 34.8% fewer patients required tumor MMR testing and 28.6% fewer required analyses of MMR variants, resulting in a 4.9% rate of missed Lynch syndrome cases.

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

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promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM variants with Lynch-like disease in families. 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. 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).

Bouzourene et al (2010) analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC and 16 patients with Lynch syndrome. A BRAF variant was not found in any of the Lynch syndrome patients. MLH1 promoter methylation was only present in 1 Lynch syndrome patient. However, 8 of the 11 sporadic CRC patients had the BRAF variant, and all 11 patients were MLH1 methylated, suggesting patients with BRAF variants could be excluded from germline testing for Lynch syndrome. Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients. 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. The authors detected BRAF-mutated CRC with 100% sensitivity and 98.8% specificity. 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.

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. Risks do not appear to appreciably increase until after age 40. In a prospective study by Leenen et al (2012), 179 consecutive endometrial cancer patients 70 years of age or younger were analyzed for MSI, using IHC for expression of 4 MMR proteins, MMR gene methylation status, and BRAF variants. Results are presented in Table 3; 92% of patients were older than 50 years of age.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N</th>
<th>Percent (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsatellite stable and normal protein staining</td>
<td>137</td>
<td>76</td>
</tr>
<tr>
<td>MSI-H and MLH1 absent</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Sporadic MSI-H</td>
<td>31</td>
<td>17 (13 to 24)</td>
</tr>
<tr>
<td>Likely to have Lynch syndrome</td>
<td>11</td>
<td>6 (3 to 11)</td>
</tr>
<tr>
<td>Variant-positive</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N</th>
<th>Percent (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No variant found</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Refused further DNA testing</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

MSI-H: high microsatellite instability.

**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**

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 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 the Amsterdam or Revised Bethesda criteria or risk prediction scores 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 in 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.
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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.

1. The 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 MMR variant.

2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. 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.

3. 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 (ie, the index patient).
   1. Subtotal colectomy is recommended as an alternative to segmental resection but has not been shown superior in follow-up studies
   2. 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.
   3. Surveillance and prevention for other Lynch syndrome cancers:
      1. 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.
      2. 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. 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.
      3. 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.

In early documentation of the natural history of CRC in highly selected families with a strong history of hereditary CRC, Fitzgibbons et al (1987) indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, in those with CRC. As a result, the Cancer Genetic Studies Consortium...
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(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. Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. Van Dalen et al (2003) suggested that subtotal colectomy with ileorectal anastomosis markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance. A 2003 mathematical model comparing total colectomy plus ileorectal anastomosis with hemicolectomy estimated increased life expectancies of 2.3, 1, and 0.3 years for ages 27, 47, and 67, respectively; for stage I cancer, estimated life expectancies for the same ages were 3.4, 1.5, and 0.4, respectively. Based on this work, the 2006 joint American Society of Clinical Oncology and Society of Surgical Oncology review assessing risk-reducing surgery in hereditary cancers recommended offering both options to patients with Lynch syndrome and CRC, especially those who are younger. 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.

Table 4 summarizes the clinical utility studies assessing genetic testing for Lynch syndrome.

Table 4. Summary of Clinical Validity Studies for Genetic Testing for Lynch Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yurgelun et al (2012)</td>
<td>Prospective cohort: Examined uptake of risk-reducing strategies in 40 women at risk for LS-associated endometrial cancer. Cross-sectional cohort: Examined adoption of risk-reduction strategies using a one-time questionnaire in 77 women at risk of LS-associated endometrial cancer.</td>
<td>In cross-sectional cohort, 58/77 (75%) women reported engaging in endometrial cancer risk-reduction. Proportion of women engaging in endometrial cancer risk-reduction strategy before genetic testing: 26/40 (65%). At 1-y follow-up, 16/16 (100%) MMR variant carriers were adherent to guidelines for risk-reduction, 9 (56%) of whom had a prophylactic hysterectomy. By 3 y, 11/16 (69%) MMR variant carriers had a prophylactic hysterectomy. Among women with negative or uninformative genetic test results, none had a prophylactic hysterectomy after testing.</td>
</tr>
<tr>
<td>Engel et al (2010)</td>
<td>Prospective cohort: Assessed efficacy of annual colonoscopic surveillance in 1126 at-risk individuals from families with LS</td>
<td>99 CRCs found in 90 individuals; 71 were diagnosed by surveillance colonoscopies. Median time between CRCs detected through follow-up colonoscopy and preceding colonoscopy was 11.3 mo.</td>
</tr>
<tr>
<td>Järvinen et al (2009)</td>
<td>Observational; 609 individuals from 57 LS families; 242 variant-positive and 367 variant-negative followed for cancer incidence over a mean of 11.5 y</td>
<td>No increase in cancer mortality in variant-positive vs -negative individuals; 74 variant-positive individuals had adenomas removed; 48 variant-positive women had prophylactic hysterectomy</td>
</tr>
<tr>
<td>Dove-Edwin et al (2005)</td>
<td>Prospective observational; 554 individuals from 290 at-risk families with HNPCC or MMR variants followed for 16 y</td>
<td>Estimated 72% decrease in CRC death in screened individuals</td>
</tr>
</tbody>
</table>
Study Design and Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vos tot Nederveen et al (2002)</td>
<td>Observational; 857 at-risk individuals from 114 HNPCC- or MMR-positive families.</td>
<td>10-y cumulative risk of CRC, 15.7% vs 3.4% for partial vs subtotal colectomy</td>
</tr>
<tr>
<td>Syngal et al (1998)</td>
<td>Decision analysis model: Assessed impact of decision about immediate prophylactic colectomy, delayed colectomy, or endoscopic surveillance at the time of a positive result on genetic testing</td>
<td>Compared with no intervention, all risk-reduction strategies led gains in life expectancy from 13.5 y for surveillance to 15.6 y for prophylactic proctocolectomy at 25 y of age. Also, surveillance led to QALY gain of 3.1 y vs 0.3 y with subtotal colectomy.</td>
</tr>
</tbody>
</table>
| Järvinen et al (1995); Järvinen et al (2000) | Observational; 252 at-risk individuals from 20 of 22 families with MMR variants invited for colonoscopy screening every 3 y; 133 agreed; 118 declined. Of those who declined, 8 (15%) had screening examinations outside of the study. | • Screening vs nonscreening  
• Incidence of CRC: 4.5% (n=6) vs 11.9% (n=14) (p=0.03)  
• 6 vs 12 deaths within 10 y (p=0.08) |

CRC: colorectal cancer; HNPCC: hereditary nonpolyposis colorectal cancer; LS: Lynch syndrome; MMR: mismatch repair; QALY: quality of life adjusted years.

Table 5. Modeling of Endometrial Cancer Screening Strategies for Detecting Lynch Syndrome

<table>
<thead>
<tr>
<th>Testing Strategy</th>
<th>No. Cases Subject to IHC Triage</th>
<th>No. Identified With Lynch Syndrome</th>
<th>No. Subsequent CRC Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam II criteria</td>
<td>NA</td>
<td>539</td>
<td>2582</td>
</tr>
<tr>
<td>Age &lt;50 y, and at least 1 FDR (Lynch-associated cancer)</td>
<td>NA</td>
<td>530</td>
<td>2470</td>
</tr>
<tr>
<td>IHC triage &lt;age 50 y</td>
<td>6285</td>
<td>520</td>
<td>2442</td>
</tr>
<tr>
<td>IHC triage &lt;age 60 y</td>
<td>16,226</td>
<td>548</td>
<td>2450</td>
</tr>
<tr>
<td>IHC triage at any age; at least 1 FDR with Lynch-associated cancer</td>
<td>5786</td>
<td>755</td>
<td>2442</td>
</tr>
<tr>
<td>IHC triage all endometrial cancers</td>
<td>45,000</td>
<td>827</td>
<td>2413</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; FDR: first-degree relative; IHC: immunohistochemical; NA: not available.

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 another retrospective cohort study, Obermair et al (2010) found that hysterectomy improved survival among female colon cancer survivors with Lynch syndrome. This study also 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. Data on variant-specific risks have suggested that prophylactic gynecologic surgery benefits for carriers of MSH6 variants may offer less obvious benefits compared with harms, because the lifetime risk of endometrial cancer is lower than for carriers of MLH1 or MSH2 variants, and the lifetime risk of ovarian cancer is similar to the risk for the general population.
However, for carriers of the *EPCAM* deletion, 3 studies (2011, 2012) reported on 3 cases of endometrial cancer in 103 female carriers who did not undergo a preventative hysterectomy. Women with *EPCAM* deletions consequently have a 1-fold lower lifetime risk of developing endometrial cancer than with carriers with an MMR variant. This might support a clinical management scenario rather than prophylactic surgery. An alternative to prophylactic surgery is surveillance for endometrial cancer using transvaginal ultrasound and endometrial biopsy. Evidence has suggested that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet has indicated surveillance reduces mortality due to endometrial cancer. Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.

**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 PICOTS were used to select literature to inform this review.

**Patients**

The relevant populations of interest are 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 *ASATK11* (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 (eg, 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.

Timing
Genetic testing for SMAD4 and BMPR1 (for JPS) and ASATK11 (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.

Setting
Ordering and interpreting genetic testing may be complex and is best done by experienced specialists such as gastroenterologists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria
For the evaluation of 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 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 6 summarizes the clinical utility studies assessing genetic testing for JPS and PJS.
Table 6. Summary of Clinical Validity Studies Assessing Genetic Testing for JPS and PJS

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2010)</td>
<td>Observational; 17 clinically diagnosed children with PJS</td>
<td>STK11 variants detected in 29.4% (5/17)</td>
</tr>
<tr>
<td>Calva-Cerqueira et al (2009)</td>
<td>Observational; 102 unrelated JPS probands analyzed all of whom met clinical criteria for JPS</td>
<td>SMAD4 and BMPR1A variants detected in 41% (42/102) JPS probands</td>
</tr>
<tr>
<td>Aretz et al (2007)</td>
<td>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</td>
<td>SMAD4 and BMPR1A variants detected in 60% of typical JPS patients and none in presumed JPS patients; overall diagnostic yield, 49%</td>
</tr>
<tr>
<td>Volikos et al (2006)</td>
<td>Observational; 76 clinically diagnosed with PJS</td>
<td>Detection rate of germline variants was about 80% (59/76)</td>
</tr>
<tr>
<td>Aretz et al (2005)</td>
<td>Observational; 71 patients (56 met clinical criteria for PJS; 12 presumed to have PJS)</td>
<td>STK11 variant detected in 52% (37/71)</td>
</tr>
</tbody>
</table>

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 for JPS and PJS have been reported to be between 60% and 41% and 29.4% and 80%, respectively.

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 in emotional burden.

Table 7 summarizes clinical utility studies assessing genetic testing for JPS and PJS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aytac et al (2015)</td>
<td>Observational: 35 patients had germline variants in <em>BMPR1A</em> (8 patients) or <em>SMAD4</em> (27) with a median follow-up of 11 y</td>
<td>No patient was diagnosed with cancer in the <em>BMPR1A</em> group, whereas 4 men with a <em>SMAD4</em> variant developed GI (n=3) or extraintestinal (n=1) cancer. The GI cancer risk in patients with JPS and a <em>SMAD4</em> variant was 11% (3/27).</td>
</tr>
<tr>
<td>Resta et al (2013)</td>
<td>Observational: 119 patients with PJS</td>
<td>Cancer occurred in 31/119 patients (RR for overall cancer risk, 15.1); mean age at first cancer diagnosis was 41 y. Kaplan-Meier estimates for overall cumulative cancer risks were 20%, 43%, 71%, and 89%, at age 40, 50, 60, and 65 y, respectively.</td>
</tr>
<tr>
<td>Lier et al (2010)</td>
<td>Systematic review: 21 original articles, 20 cohort studies, and 1 meta-analysis (total N=1644 PJS patients)</td>
<td>349 patients developed 384 malignancies at average age of 42 y. Lifetime risk for any cancer varied between 37% and 93% with RR ranging from 9.9 to 18 vs the general population.</td>
</tr>
<tr>
<td>Salloch et al (2009)</td>
<td>Observational: 31 patients with PJS; <em>STK11</em> variants in 16/22 families</td>
<td>10 carcinomas detected in 6 patients resulting in a cancer risk of 65% up to the age of 65 y; surveillance strategy detected 50% of cancers (n=5) at an early potentially curable stage</td>
</tr>
<tr>
<td>Brosens et al (2007)</td>
<td>Observational: 84 patients with JPS contributing 1652.2 person-years of follow-up vs general population of the U.S. (SEER data)</td>
<td>RR of CRC was 34.0 (95% CI: 14.4 to 65.7); cumulative life-time risk for CRC was 38.7%; mean age of diagnosis of CRC, 43.9 y</td>
</tr>
</tbody>
</table>

CI: confidence interval; CRC: colorectal cancer; GI: gastrointestinal; JPS: juvenile polypsis syndrome; PJS: Peutz-Jeghers syndrome; RR: relative risk.

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 \textit{APC}, or are at-risk relatives of patients with FAP who receive genetic testing for \textit{MUTYH} after a negative \textit{APC} test result, the evidence includes a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. For patients with an \textit{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 \textit{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 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 the Amsterdam or Revised Bethesda criteria who receive genetic testing for MMR genes, the evidence includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in CRC. Relevant outcomes are overall survival, 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 \textit{EPCAM} variants, the evidence includes variant prevalence studies and case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown an association between \textit{EPCAM} variants and Lynch-like disease in families, and the cumulative risk for CRC is similar to carriers of an \textit{MSH2} variant. Identification of an \textit{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 overall survival, 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 overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between $SMAD4$ and $BMPR1A$ and $STK11$ variants with JPS and PJS, respectively. Direct evidence of clinical utility for genetic testing of a JPS or PJS is not available. Genetic testing may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

References

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Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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Original Effective Date: 10/16/2006
Current Effective Date: 11/21/2018


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04/05/2006 Medical Director review
04/19/2006 Medical Policy Committee review
06/13/2007 Medical Director review
06/20/2007 Medical Policy Committee approval. Added statement to consider investigational when patient selection criteria are not met.
10/10/2007 Medical Director review
10/17/2007 Medical Policy Committee approval. No change to policy statement.
10/01/2008 Medical Director review
10/22/2008 Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009 Medical Policy Committee review
10/14/2009 Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010 Medical Policy Committee review
10/20/2010 Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/06/2011 Medical Policy Committee review
10/19/2011 Medical Policy Implementation Committee approval. Policy revised extensively to track BCBSA.
11/01/2012 Medical Policy Committee review
01/23/2013 Coding updated
01/09/2014 Medical Policy Committee review
01/15/2014 Medical Policy Implementation Committee approval. Policy title revised from “Genetic Testing for Inherited Susceptibility to Colon Cancer Including Microsatellite Instability Testing” to “Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes” since Lynch syndrome is not a polyposis syndrome. Added that BRAF V600E or MLH1 promoter methylation may be considered eligible for coverage when MLH1 is not expressed in the tumor on IHC analysis. Added that testing for all other gene mutations for Lynch syndrome or colorectal cancer is considered investigational.
05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. Added the words “a patient with” to the guidelines.
04/02/2015 Medical Policy Committee review
04/20/2015 Medical Policy Implementation Committee approval. Bethesda Guidelines clarified. Added to eligibility statement for MMR gene mutation testing “Patients with ≥5% risk of Lynch Syndrome on one of the following mutation prediction models: MMRpro, PREMM1,2,6, or MMRpredict.”
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016 Coding update
04/07/2016 Medical Policy Committee review
04/20/2016 Medical Policy Implementation Committee approval. No changes to coverage eligibility.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. No changes to coverage eligibility.
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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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