Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy Number: 2.04.08  Last Review: 1/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for genetic testing for Lynch Syndrome and inherited intestinal polyposis syndromes when it is determined to be medically necessary because the criteria shown below are met.

Note: Genetic testing may be excluded in some contracts. Verify benefits prior to review of Medical Necessity.

When Policy Topic is covered
Genetic testing for APC gene variants may be considered medically necessary in the following patients:
- At-risk relatives (see Considerations) of patients with FAP and/or a known APC variant.
- Patients with a differential diagnosis of attenuated FAP vs. MYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC variants or screening for MMR variants depends upon clinical presentation.

Genetic testing for MUTYH gene variants may be considered medically necessary in the following patients:
- Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome and a negative result for APC gene variants. Family history of no parents or children with FAP is consistent with MUTYH-associated polyposis (autosomal recessive).

Genetic testing for MMR genes (MLH1, MSH2, MSH6, PMS2) is considered medically necessary in the following patients:
- Patients with colorectal cancer, for the diagnosis of Lynch syndrome (See Considerations).
Patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer (see Considerations), for the diagnosis of Lynch syndrome.

- At-risk relatives (see Considerations) of patients with Lynch syndrome with a known MMR variant.
- Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC variants or screening for MMR variants depends upon clinical presentation.
- Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR variants.

Genetic testing for EPCAM variants is considered medically necessary when any one of the following 3 major criteria (solid bullets) are met:

- Patients with colorectal cancer, for the diagnosis of Lynch syndrome (see Considerations Section) when:
  - Tumor tissue shows lack of MSH2 expression by immunohistochemistry and patient is negative for a germline variant in MSH2; or
  - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in MSH2, MLH1, PMS2, and MSH6; OR
- At-risk relatives (see Considerations) of patients with Lynch syndrome with a known EPCAM variant. OR
- Patients without colorectal cancer 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.

Genetic testing for BRAF V600E or MLH1 promoter methylation may be considered medically necessary to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

**SMAD4 and BMPR1A Testing**

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:

- 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**

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

- Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 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.

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

**When Policy Topic is not covered**

Genetic testing for APC gene variants is **not medically necessary** for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

Genetic testing for all other gene variants for Lynch syndrome or colorectal cancer is considered **investigational**.

**Considerations**

Due to the high lifetime risk of cancer of the majority of the 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.

It is recommended that, when possible, initial genetic testing for FAP or Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the variant found in the affected family member. (See Benefit Application section.)

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 Caucasian populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

For patients with colorectal cancer 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 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.

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 (eg, 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 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.

Amsterdam II Clinical Criteria (all criteria must be fulfilled). are the most stringent criteria for defining families at high risk for Lynch Syndrome:

- 3 or more relatives with an associated cancer (colorectal cancer, 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 (FAP) should be excluded in cases of colorectal carcinoma;
- Tumors should be verified by pathologic examination.

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 2 generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years;
  o OR: 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.

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. The Bethesda guidelines are also felt to be more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years-old;
- Presence of synchronous (at the same time) or metachronous (at another time i.e.- a recurrence of) CRC or other Lynch syndrome-associated tumors\(^a\), regardless of age;
- CRC with high microsatellite instability histology diagnosed in a patient less than 60-years old;
- CRC diagnosed in one 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 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 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 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>
</tr>
</thead>
<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>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
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<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>
</tr>
</tbody>
</table>

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

**Genetic Counseling**

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

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Genetic testing for APC</td>
<td>No genetic testing</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Who are suspected of attenuated FAP, MAP, and Lynch syndrome, or are at-risk relatives of patients with FAP</td>
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<td>Disease-specific survival</td>
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<td>Test accuracy</td>
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<td>Individuals:</td>
<td>Genetic testing for MUTYH after a negative APC test result</td>
<td>No genetic testing</td>
<td>Overall survival</td>
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<tr>
<td>Who are suspected of attenuated FAP, MAP, and Lynch syndrome</td>
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### Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes 2.04.08

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<tr>
<td>Who are suspected of attenuated FAP, MAP, and Lynch syndrome; CRC; or endometrial cancer and first-degree relative with Lynch</td>
<td>Genetic testing for MMR genes</td>
<td>No genetic testing</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
</tr>
<tr>
<td>Who are at-risk relatives of patients with Lynch or family history meeting appropriate criteria, but do not have CRC</td>
<td>Genetic testing for MMR genes</td>
<td>No genetic testing</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
</tr>
<tr>
<td>Who warrant Lynch testing, screen negative on MMR testing, but positive for MSI and lack MSH2 protein expression</td>
<td>Genetic testing for EPCAM variants</td>
<td>No genetic testing</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
</tr>
<tr>
<td>With CRC in whom MLH1 protein is not expressed on immunohistochemical analysis</td>
<td>Genetic testing for BRAF V600E or MLH1 promoter methylation</td>
<td>No genetic testing</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
</tr>
<tr>
<td>Who are suspected of juvenile polyposis syndrome or are at-risk relatives of patients suspected of or diagnosed with JPS</td>
<td>Genetic testing for SMAD4 and BMPR1A genes</td>
<td>No genetic testing</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
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<tr>
<td>Who are suspected of Peutz-Jeghers syndrome or are at-risk relatives of patients suspected of or diagnosed with PJS</td>
<td>Genetic testing for STK11 gene</td>
<td>No genetic testing</td>
<td>Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
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CRC: colorectal cancer; FAP: familial adenomatous polyposis; MAP: MUTYH-associated polyposis; MMR: mismatch repair; MSI: microsatellite instability.

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 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, and Peutz-Jeghers syndrome.

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, 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 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 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 colorectal cancer (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 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 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 overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between \textit{BRAF} V600E variant and \textit{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 juvenile polyposis syndrome or Peutz-Jeghers syndrome or (2) are at-risk relatives of patients suspected of or diagnosed with juvenile polyposis syndrome or Peutz-Jeghers syndrome who receive genetic testing for \textit{SMAD4}, \textit{BMPR1A}, or \textit{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 \textit{SMAD4} and \textit{BMPR1A} and \textit{STK11} variants with juvenile polyposis syndrome and Peutz-Jeghers syndrome, respectively. Direct evidence of clinical utility for genetic testing of a juvenile polyposis syndrome or Peutz-Jeghers syndrome 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.

\textbf{Background}
\textbf{Hereditary Colorectal Cancers}
Currently, 2 types of hereditary colorectal cancers (CRC) 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.

\textbf{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 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 adenomatous polyposis coli (\textit{APC}) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Variants in the \textit{APC} gene result in altered protein length in about 80\% to 85\% of cases of FAP. A specific \textit{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 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. 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:

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

**Lynch Syndrome**

Lynch syndrome is an inherited disorder that results in a higher predisposition to CRC and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3% to 5% of all CRC. People with Lynch syndrome have a 70% to 80% lifetime risk of developing any type of cancer. However the risk varies by genotype. It occurs as a result of germline variant in the 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 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. 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.
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 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”.6

The second phenotype screening test is IHC, which involves the staining of tumor tissue for the presence of 4 MMR proteins (MLH1, MSH2, MSH6, PMS2). The absence of 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.\textsuperscript{7,8} IHC screening has sensitivity for \textit{MLH1}, \textit{MSH2}, and \textit{MSH6} of about 83% and a specificity of about 90% for each.

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

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

Recently, novel deletions have been reported to affect the expression of the \textit{MSH2} gene in the absence of an \textit{MSH2} gene variant, and thereby cause Lynch syndrome. In these cases, deletions in \textit{EPCAM}, the gene for the epithelial cell adhesion molecule, are responsible. \textit{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 \textit{MSH2} expression, but no \textit{MSH2} variant is found by sequencing. \textit{EPCAM} is found just upstream, in a transcriptional sense, of \textit{MSH2}. Deletions of \textit{EPCAM} that encompass the last 2 exons of the \textit{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 \textit{MSH2} promoter. This hypermethylation prevents normal \textit{MSH2} protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an \textit{MSH2} variant prevents \textit{MSH2} gene expression. Several studies have characterized such \textit{EPCAM} deletions, established their correlation with the presence of \textit{EPCAM-MSH2} fusion messenger RNAs (apparently nonfunctional) and with the presence of \textit{MSH2} promoter hypermethylation, and, most importantly, have shown the cosegregation of these \textit{EPCAM} variants with Lynch-like disease in families.\textsuperscript{11-16}

Distinct from patients with \textit{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,” ie, methylation of promoter regions that control the expression of the MMR genes.\textsuperscript{11,17,18} 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\(^{19}\) (low sensitivity but high specificity), Revised Bethesda guidelines\(^{20}\) (better sensitivity but poorer specificity), and risk prediction models (eg, MMRpro; PREMM5; MMRpredict).\(^{21}\) 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 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.\(^{22}\) Approximately 60% of patients with JPS have a germline variant in the $BMPR1A$ gene or the $SMAD4$ gene.\(^{23,24}\) Approximately 25% of patients have de novo variants.\(^{25,26}\) In most cases, polyps appear in the first decade of life and most patients are symptomatic by age 20 years.\(^{27}\) 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.22,26,27

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.28,29 The estimated lifetime risk of gastric cancer is 20% to 30%, with a mean age at diagnosis of 58 years.22,26,28 JPS may also be associated with hereditary hemorrhagic telangiectasia.30 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.31 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.31

**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 *STK11 (LKB1)* gene is responsible for PJS, which has a high penetrance of over 90% by the age of 30 years.32-34 However, 10% to 20% of individuals with PJS have no family history and are presumed to have PJS due to de novo variants.35 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.36 The estimated lifetime risk of gastrointestinal cancer ranges from 38% to 66%.36 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 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.31 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.

**Rationale**
This evidence review was created in April 1998 and has been regularly updated with searches of the MEDLINE database. The most recent literature review was performed through July 9, 2018.

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

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

**Genetic Testing for Familial Adenomatous Polyposis and MUTYH-associated polyposis**

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

- Identify at-risk relatives of 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 PICOTS were used to select literature to inform this review.

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

**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:
- 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)\(^3\) 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</td>
<td>Observational:195 confirmed cases of FAP</td>
<td>Cumulative risk of rectal cancer</td>
</tr>
</tbody>
</table>
### Study Design and Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2000)(^54)</td>
<td>mortality was 7% at 20 y postsurgery and cumulative mortality was 11.1% at the age of 70 y, indicating a substantial risk of developing cancer even after surgery</td>
</tr>
<tr>
<td>Järvinen (1992)(^55)</td>
<td>65.5% of symptomatic cases had CRC vs 6.6% cases among those screened during family screening</td>
</tr>
<tr>
<td>Vasen et al (1990)(^56)</td>
<td>47% of symptomatic cases had CRC at a mean age of 35 y vs 4% at 24 y</td>
</tr>
</tbody>
</table>

**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 mismatch repair (MMR) variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria
- Make a differential diagnosis of attenuated FAP v 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 (eg, 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>
<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 (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 95.5)</td>
<td>95.5 (95 CI, 94.7 to 97.2)</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 promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM variants with Lynch-like disease in families.11-16 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.60 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.10 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.61 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.62 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.63
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 3. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome

<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>
<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.

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.\(^{23}\)

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.\(^{10}\) Transvaginal ultrasound is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, transvaginal ultrasound in conjunction with endometrial biopsy has been recommended for surveillance.

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.\(^{24}\) As a result, 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.\(^{25}\) 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.\(^{26}\) 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.\(^{27}\) 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.\(^{28}\) 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>
<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 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>
<tr>
<td>De Vos tot Nederveen Cappel 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.

Kwon et al (2011) developed a Markov Monte Carlo simulation model to compare 6 strategies for Lynch syndrome testing in women with endometrial cancer. Overall, the results suggested that IHC triage of women at any age who had at least 1 first-degree relative with a Lynch-associated cancer was the most effective strategy for identifying Lynch syndrome and subsequent CRC cases. The model used published prevalence estimates of Lynch syndrome in all endometrial cancer patients of 2% (range, 1%-3%), and of 17% (range, 15%-20%) in endometrial cancer patients with at least 1 first-degree relative with a Lynch-associated cancer. Results are presented in Table 5.

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. \textsuperscript{91} Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival. \textsuperscript{91}

\textbf{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.

\textbf{Genetic Testing for Juvenile polyposis syndrome and Peutz-Jeghers syndrome:}

\textbf{Clinical Context and Test Purpose}

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

- To confirm a diagnosis of JPS or PJS in 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.

\textbf{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.

\textbf{Interventions}

The relevant intervention is genetic testing for \textit{SMAD4} and \textit{BMPR1} (for JPS) and \textit{ASATK11} (for PJS). Commercial testing is available from numerous companies.

\textbf{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 \textit{SMAD4} and \textit{BMPR1} (for JPS) and \textit{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>\textit{STK11} variants detected in 29.4% (5/17)</td>
</tr>
</tbody>
</table>
Study | Study Design and Population | Results |
--- | --- | --- |
Calva-Cerqueira et al (2009) | 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) | 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) | Observational; 76 clinically diagnosed with PJS | Detection rate of germline variants was about 80% (59/76) |
Aretz et al (2005) | 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 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 7. Summary of Clinical Utility Studies for 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 <strong>BMPR1A</strong> (8 patients) or <strong>SMAD4</strong> (27) with a median follow-up of 11 y</td>
<td>No patient was diagnosed with cancer in the <strong>BMPR1A</strong> group, whereas 4 men with a <strong>SMAD4</strong> variant developed GI (n=3) or extraintestinal (n=1) cancer. The GI cancer risk in patients with JPS and a <strong>SMAD4</strong> 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 RRs 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; <strong>STK11</strong> 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 polyposis 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 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, 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 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 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 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 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.

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 (NCCN) guidelines (v.1.2018) are summarized in Table 8.

### Table 8. Criteria for Evaluation of Lynch Syndrome

**Criteria for the Evaluation of Lynch Syndrome**

<table>
<thead>
<tr>
<th>Known LS variant in the family</th>
<th>An individual with colorectal or endometrial cancer and any of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Diagnosed &lt;50 y</td>
</tr>
<tr>
<td></td>
<td>• Another synchronous or metachronous LS-related cancer&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• ≥1 first-degree or second-degree relative with LS-related&lt;sup&gt;a&lt;/sup&gt; cancer diagnosed &lt;50 y</td>
</tr>
<tr>
<td></td>
<td>• ≥2 first-degree or second-degree relatives with LS-related&lt;sup&gt;a&lt;/sup&gt; cancers regardless of age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>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&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of any of the following:</td>
</tr>
<tr>
<td>• ≥1 first-degree relative with colorectal or endometrial cancer diagnosed &lt;50 y</td>
</tr>
<tr>
<td>• ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>• ≥2 first-degree or second-degree relatives with LS-related cancer,&lt;sup&gt;a&lt;/sup&gt; including ≥1 diagnosed &lt;50 y</td>
</tr>
<tr>
<td>• ≥3 first-degree or second-degree relatives with LS-related cancers,&lt;sup&gt;a&lt;/sup&gt; regardless of age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>An individual with a LS-related cancer&lt;sup&gt;a&lt;/sup&gt; or unaffected individual with ≥5% risk&lt;sup&gt;c&lt;/sup&gt; of having an MMR gene variant based on predictive models (PREMM5, MMRpro, MMRpredict)</th>
</tr>
</thead>
<tbody>
<tr>
<td>An individual with a colorectal tumor with MSI-high histology (ie, presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) diagnosed ≤60 y</td>
</tr>
</tbody>
</table>

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

<sup>a</sup>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.

<sup>b</sup>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.

<sup>c</sup>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, NCCN guidelines (v.2.2018) recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years. Genetic testing is recommended for at-risk family members of patients with positive variants in *MLH1, MSH2, MSH6*, and *PMS2*. 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.
NCCN guidelines for colon cancer (v.3.2018)\textsuperscript{101} and for CRC screening (v.3.2018)\textsuperscript{102} recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year postsurgery and, if normal, again in 3 years, then every 5 years based on findings. However, because of the high likelihood of cancer, colonoscopy is recommended every 1 to 2 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.\textsuperscript{83} NCCN guidelines on genetic/familial high-risk assessment for colorectal indicate for \textit{MLH1}, \textit{MSH2}, and \textit{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.”\textsuperscript{31} “\textit{MSH6} variant carriers should begin surveillance with colonoscopy at age 30 to 35 years, and \textit{PMS2} carriers should begin surveillance at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 years for \textit{MSH6} and \textit{PMS2} variant carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years.” “If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered.”

NCCN guidelines for colon cancer recommend that patients 70 years or younger plus those older than 70 years of age who meet the Bethesda guidelines be tested for the mismatch repair (MMR) protein for possible Lynch syndrome.\textsuperscript{101} These guidelines also indicate all colon cancer patients should be questioned about family history and considered for risk assessment as per NCCN colorectal screening guidelines. NCCN guidelines for uterine neoplasm also recommend universal screening for MMR genes.\textsuperscript{100}

There are limited data on the efficacy of various screening modalities in juvenile polyposis syndrome and Peutz-Jeghers syndrome. NCCN cancer risk and surveillance 2 category 2A recommendations for these indications are summarized in Tables 9 and 10.\textsuperscript{31}

\textbf{Table 9. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome}\\

<table>
<thead>
<tr>
<th>Site</th>
<th>Lifetime Risk, %</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>45-50</td>
<td>• Mammogram and breast MRI annually</td>
<td>≈25 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical breast exam every 6 mo</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>39</td>
<td>Colonoscopy every 2-3 y</td>
<td>Late teens</td>
</tr>
<tr>
<td>Stomach</td>
<td>29</td>
<td>Upper endoscopy every 2-3 y</td>
<td>Late teens</td>
</tr>
<tr>
<td>Small intestine</td>
<td>13</td>
<td>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)</td>
<td>≈8 to 10 y</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11-36</td>
<td>Magnetic resonance cholangiopancreatography with contrast or endoscopic ultrasound every 1-2 h</td>
<td>≈30 to 35 y</td>
</tr>
<tr>
<td>Ovary (typically benign sex)</td>
<td>18-21</td>
<td>• Pelvic examination and Pap smear</td>
<td>≈18 to 20</td>
</tr>
</tbody>
</table>

NCCN guidelines for uterine neoplasm also recommend universal screening for MMR genes.


<table>
<thead>
<tr>
<th>Site</th>
<th>Lifetime Risk, %</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>40-50</td>
<td>Colonoscopy every year if polyps are found and every 2-3 y if no polyps are found&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≈15 y</td>
</tr>
<tr>
<td>Stomach</td>
<td>21 if multiple polyps</td>
<td>Upper endoscopy annually if polyps are found and every 2-3 y if no polyps are found&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≈15 y</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Rare, undefined</td>
<td>No recommendations made</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>Rare, undefined</td>
<td>No recommendations made</td>
<td></td>
</tr>
<tr>
<td>HHT</td>
<td>Undefined</td>
<td>In individuals with SMAD4 variants, screen for vascular lesions associated with HHT</td>
<td>Within first 56 mo of age</td>
</tr>
</tbody>
</table>

HHT: hereditary hemorrhagic telangiectasia.

<sup>a</sup> In families without an identified genetic variant, consider substituting endoscopy every 5 y beginning at age 20 and every 10 y beginning at age 40 y in patients in whom no polyps are found.

**Table 10. Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome**

**American College of Gastroenterology**

The American College of Gastroenterology (2015) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.26

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.103
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). 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.

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

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 11.

**Table 11. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>Unpublished</td>
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<td></td>
</tr>
<tr>
<td>NCT01646112</td>
<td>Living in Lynch Syndrome Limbo: Exploring the</td>
<td>34</td>
<td>Feb 2016 (completed)</td>
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<tr>
<td></td>
<td>Meaning of Uncertain Genetic Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01850654</td>
<td>Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome</td>
<td>4000</td>
<td>Sep 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**References**


### Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81210</td>
<td>BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promotor methylation analysis</td>
</tr>
<tr>
<td>81292</td>
<td>MLH1 (mutl.homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81293</td>
<td>MLH1 (mutl.homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81294</td>
<td>MLH1 (mutl.homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81295</td>
<td>MSH2 (mutS.homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81296</td>
<td>MSH2 (mutS.homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
</tbody>
</table>
analysis; known familial variants

81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81299 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81300 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT 25, BAT 26), includes comparison of neoplastic and normal tissue, if performed

81317 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch Syndrome) gene analysis; full sequence analysis

81318 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch Syndrome) gene analysis; known familial variants

81319 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch Syndrome) gene analysis; duplication/deletion variants

81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, variant scanning or duplication/deletion variants of 2-5 exons)

81435 Hereditary colon cancer disorders (eg, 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

81436 Hereditary colon cancer disorders (eg, 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

ICD-10 Codes

Z85.030- Z85.038 Personal history of malignant neoplasm of large intestine; code range

Z85.040- Z85.048 Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus; code range

Z80.0 Family history of malignant neoplasm of digestive organs

Z31.5 Encounter for genetic counseling
C18.0- C18.9  Malignant neoplasm of colon; code range
C19  Malignant neoplasm of rectosigmoid junction
C20  Malignant neoplasm of rectum
D12.0- D12.9  Benign neoplasm of colon, rectum, anus and anal canal; code range
D01.0- D01.9  Carcinoma in situ of other and unspecified digestive organs; code range

Effective in 2012, there are specific CPT codes for genetic testing of MLH1, MSH2, MSH6, PMS2 and microsatellite instability.

Prior to 2012, there were no specific CPT codes for genetic testing; testing was typically coded for using a series of CPT codes describing the individual steps in the testing process. CPT codes 83890-83898 described the preparation of DNA for analysis, single strand conformation polymorphisms, heteroduplex, denaturing gradient gel electrophoresis (all CPT code 83903); variant identification by sequencing (83904); variant identification by allele specific transcription (83905) or translation (83906). The exact methodology used will depend on the clinical situation. For example, genetic testing for a single known variant involves fewer steps than the testing required to identify one of many possible variants.

Genetic Testing in Patients at Risk for Lynch Syndrome:
83890: Molecular diagnostics: molecular isolation or extraction; each nucleic acid type (i.e., DNA or RNA)
83894: Molecular diagnostics: separation by gel electrophoresis (e.g., agarose, polyacrylamide), each nucleic acid preparation
83898: Molecular diagnostics: amplification, target, each nucleic acid sequence
83902: Molecular diagnostics: reverse transcription
83912: Molecular diagnostics: interpretation and report

Genetic Testing in Patients at Risk for FAP:
83890: Molecular diagnostics: molecular isolation or extraction; each nucleic acid type (i.e., DNA or RNA)
83892: Molecular diagnostics: enzymatic digestion; each enzyme treatment
83894: Molecular diagnostics: separation by gel electrophoresis (e.g., agarose, polyacrylamide), each nucleic acid preparation
83898: Molecular diagnostics: amplification, target, each nucleic acid sequence
83902: Molecular diagnostics: reverse transcription
83912: Molecular diagnostics: interpretation and report

There are CPT genetic testing modifiers specific to MLH1 (-0J), and MSH2, MSH6 or PMS2 (-0K).

There was a series of 4 HCPCS codes (see coding section below) that specifically describe genetic sequencing for MLH1 and MSH2, individually or together, or genetic testing for a single variant in a known affected family. Therefore, these codes could have been used in lieu of using CPT coding for the individual components of genetic testing.
Genetic testing for colon cancer is not widely available and is most commonly performed by commercial reference labs or research labs dedicated to genetic testing in general.

Associated genetic counseling performed by a trained genetic counselor would be coded using CPT code 96040 (Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family). Genetic counseling performed by a physician is coded using the appropriate CPT evaluation and management codes.

**Additional Policy Key Words**

Colaris

**Policy Implementation/Update Information**

1/1/04  New policy added to the Medical and Laboratory sections.
1/1/05  No policy statement changes.
1/1/06  No policy statement changes.
1/1/07  The second policy statement in the section titled When Policy Topic Is Covered, was modified slightly to include the words “...with a history of...”
1/1/08  No policy statement changes.
1/1/09  No policy statement changes.
1/1/10  Policy statements changed to indicate that testing the index patient with APC is considered not medically necessary. Intent of other policy statements generally unchanged, although requirement for positive family history no longer required for testing.
1/1/11  No policy statement changes.
1/1/12  Policy revised to add medically necessary indication for testing for EPCAM variants in patients with colorectal cancer and negative MMR variants. Coding updated.
1/1/13  Additional medically necessary indication added for patients with endometrial cancer and one first-degree relative diagnosed with a Lynch associated cancer. CPT coding updated. Title changed from Genetic Testing for Inherited Susceptibility to Colon Cancer Including Microsatellite Instability
1/1/14  Policy statement added that BRAF V600E or MLH1 promoter methylation may be considered medically necessary when MLH1 is not expressed in the tumor on IHC analysis. Added policy statement indicating testing for all other gene variants for Lynch syndrome or colorectal cancer is considered investigational.
4/1/14  Removed deleted codes S3833, S3834.
1/1/15  Revised to “Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes” since Lynch syndrome is not a polyposis syndrome. No policy statement changes.
1/1/15  Reworded criteria for Patients with colorectal cancer, for the diagnosis of Lynch syndrome in medically necessary statement.
APPENDIX

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.08

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td>X</td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variant</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are not employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.