Genetic Testing for Lynch Syndrome
And Other Inherited Colon Cancer Syndromes

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I. Description
Genetic testing is available for both those with and those at risk for various types of hereditary cancer. This review evaluates genetic testing for hereditary colorectal cancer 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 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 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 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 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.

II. Criteria/Guidelines

A. Genetic testing is covered only when testing will impact the clinical management of the patient to in terms of improving health outcomes.

B. Genetic testing for APC gene mutations is covered (subject to Limitations and Administrative Guidelines) for the following:
   1. At-risk relatives (first- or second-degrees) of patients with FAP and/or a known APC mutation.
   2. Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis (MAP) vs. Lynch syndrome. Whether testing begins with APC mutations, or screening for MMR mutations depends upon clinical presentation.
C. Genetic testing for MUTYH gene mutations is covered (subject to Limitations and Administrative Guidelines) for patients with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome and a negative test result for APC gene mutations. Family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

D. Genetic testing for mismatch repair (MMR) gene mutations is covered (subject to Limitations and Administrative Guidelines) in the following:
   1. Patients with colorectal cancer for a diagnosis of Lynch syndrome (see Policy Guidelines) ; or
   2. Patients with endometrial cancer and one first-degree relative diagnosed with a Lynch associated cancer (see Policy Guidelines) for the diagnosis of Lynch syndrome.
   3. Patients with endometrial cancer diagnosed at <50 years of age
   4. At-risk relatives (first- or second-degree) of patients with Lynch syndrome with a known MMR mutation; or
   5. Patients with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation; or
   6. Patients without colorectal cancer but with a family history meeting the Revised Bethesda or Amsterdam II criteria when no affected family members have been tested for MMR mutations.

E. Genetic testing for EPCAM mutations is covered (subject to Limitations and Administrative Guidelines) when any one of the following 3 criteria is met:
   1. Patients with colorectal cancer, for the diagnosis of Lynch syndrome (see Policy Guidelines) when:
      a. Tumor tissue shows lack of MSH2 expression by immunohistochemistry and patient is negative for a germline mutation in MSH2; or
      b. Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6; OR
   2. At risk relatives (see Policy Guidelines) of patients with Lynch syndrome with a known EPCAM mutation; OR
   3. 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 mutations, and when sequencing for MMR mutations is negative.

F. Genetic testing for BRAF V600E or MLH1 promoter methylation is covered (subject to Limitations and Administrative Guidelines) to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

G. Genetic testing for SMAD4 and BMPR1A gene variants is covered (subject to Limitations and Administrative Guidelines) when any one of the following criteria is met:
   1. Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
      a. At least 3 to 5 juvenile polyps in the colon
      b. Multiple juvenile polyps in other parts of the gastrointestinal tract
      c. Any number of juvenile polyps in a person with a known family history of juvenile polyps.
   2. At-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome.
H. Genetic testing for STK11 gene variants is covered (subject to Limitations and Administrative Guidelines) when any one of the following is met:
   1. Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
      a. Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine
      b. Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
      c. Family history of Peutz-Jeghers syndrome
   2. At-risk relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome.

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

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

Several Clinical Laboratory Improvement Amendments (CLIA)–licensed clinical laboratories offer MMR gene variant testing for Lynch syndrome. For example, the GeneTests website (available online at https://www. lists laboratories that offer this service. In at least 1 laboratory, Lynch syndrome variant testing is packaged under a 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 and 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 COLARISPLUS test includes full sequence analysis of the MLH1, MSH2, MSH6, PMS2, and MYH genes and rearrangement analysis of MLH1, MSH2, MSH6, MYH, and EPCAM using microarray comparative genomic hybridization analysis, and of PMS2 using multiplex ligation-dependent probe amplification analysis.

Similarly, GeneTests lists U. CLIA-licensed clinical laboratories that provide APC variant testing and those that provide MUTYH variant testing. The COLARIS AP test (Myriad Genetic Laboratories) includes D sequencing analysis of the APC and MUTYH genes, as well as analysis of large rearrangements in the APC gene not detected by D sequencing.
The Amsterdam II Clinical Criteria (all criteria must be met) are the most stringent criteria for defining families at high risk for Lynch syndrome:

- Three or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis)
- One should be a first-degree relative of the other two;
- Two or more successive generations affected;
- One 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 two colorectal cancers in first-degree relatives if at least two generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years; or
  - In families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

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

- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old;
- First-degree relative with a Lynch syndrome-related cancer,* with one of the cancers being diagnosed in a patient before the age of 50; or
- Presence of synchronous or metachronous CRC or other Lynch syndrome related cancer*, regardless of age; or
- CRC with high microsatellite instability histology diagnosed in a patient less than 60-years old; or
- CRC diagnosed in one or more first-degree relatives with a Lynch syndrome related cancer* with one of the cancers being diagnosed at younger than age 50 years; or
- CRC diagnosed with one or more first-degree relatives with an HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed at younger than age 50 years, OR CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumor, regardless of age.

*Lynch related cancers include colorectal, endometrial, stomach, ovarian, pancreas, ureter, and renal pelvis, biliary tract, brain (usually glioblastoma as seen Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.
IV. Limitations
   A. Genetic testing for APC gene mutations is not covered for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.
   B. Genetic testing for all other gene mutations for Lynch syndrome or colorectal cancer has not been shown to improve health outcomes.
   C. Judgment must be allowed in the case of a small family pedigree when extended family members may need to be included in the testing strategy.
   D. HMSA will only cover an affected family member who is enrolled in certain HMSA plans.
   E. Laboratories that conduct genetic testing must be CLIA-certified.
   F. Repeat testing is not covered.
   G. All references to polyps in this policy are considered to be adenomatous polyps.

V. Administrative Guidelines
   A. Precertification is required for: for genetic counseling/genetic risk assessment and genetic testing:
      1. Unaffected individuals
         a. Genetic counseling/genetic risk assessment is considered by HMSA as part of the precertification process to approve genetic testing in unaffected individuals as outlined in Criteria/Guidelines.
      2. Affected individuals
         a. BRAF, IHC or MSI testing will be covered without precertification following surgery.
         b. Genetic counseling/genetic risk assessment is required for affected individuals with positive test results for BRAF, IHC or MSI prior to further genetic testing.
         c. Genetic counseling/genetic risk assessment is required with precertification for affected individuals for whom IHC or MSI test results are unavailable and who have first or second degree relatives with Lynch-related cancer* prior to genetic testing.
         d. Genetic counseling/genetic risk assessment is required with precertification for individuals with attenuated familial adenomatous polyposis, familial adenomatous polyposis and MUTYH associated polyposis.
   B. Documentation must specify how the results of genetic testing will impact the clinical management of the patient in terms of improving health outcomes.
   C. Services must be conducted in a face-to-face consultation and/or telemedicine consult visit (in accordance with HMSA’s current telemedicine payment policy) and a subsequent consultation letter or report must be submitted to the treating physician.
   D. Services must be conducted by a properly certified/licensed and credentialed genetic specialist (i.e., board-certified medical geneticist (MD), board-certified clinical geneticist (PHD), board-certified genetic counselor (MS and/or CGC), or licensed advanced practice registered nurse in genetics (APRN)).
   E. One genetic counseling/genetic risk assessment visit after genetic testing is covered for patients who qualified for predictive genetic testing as outlined above.
   F. To precertify please complete HMSA's Precertification Request and fax or mail the form as indicated, or use iExchange. The information received should include the member's family history and a brief summary as to why the genetic test is needed.
G. If precertification is not obtained, the member will not be held responsible for payment of denied services unless an **Agreement of Financial Responsibility** is completed and signed.

**Affected** - Personal history of cancer

**Unaffected** - No personal history of cancer

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>81201-81203</td>
<td>APC genetic testing code range</td>
</tr>
<tr>
<td>81210</td>
<td>BRAF (B-raf proto-oncogene, serine/threonine kinase)(eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
</tr>
<tr>
<td>81288; 81292-81294</td>
<td>MLH1 genetic testing code range</td>
</tr>
<tr>
<td>81295-81297</td>
<td>MSH2 genetic testing code range</td>
</tr>
<tr>
<td>81298-81300</td>
<td>MSH6 genetic testing code range</td>
</tr>
<tr>
<td>81301</td>
<td>Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissues</td>
</tr>
<tr>
<td>81317-81319</td>
<td>PMS2 genetic testing code range</td>
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</tbody>
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### VI. Background

**Genetics Nomenclature Update**

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

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

**Table PG1. Nomenclature to Report on Variants Found in DNA**

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

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**
Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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

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

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

**Hereditary Colorectal Cancers**
Currently 2 well-defined types of hereditary colorectal cancer are well-defined: Familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer [HNPCC]). Lynch syndrome has been implicated in some endometrial cancers as well.

**FAP and Associated Variants**
FAP typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will go on to develop colorectal cancer (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 associated with central nervous system tumors, referred to as Turcot syndrome.

Germline mutations in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Mutations in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. A specific APC gene mutation (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 attenuated FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, CRC occurring at an average age of 50 to 55 years, but a high lifetime risk of CRC of about 70% by age 80 years. The risk of extra-intestinal cancer is lower compared with classical FAP but still high at an estimated cumulative lifetime risk of 38% compared with the general population. Only 30% or fewer of attenuated FAP patients have APC mutations; some of these patients have mutations in the MUTYH (formerly MYH) gene and are diagnosed with MUTYH-associated polyposis (MAP). MAP occurs with
a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH mutations are associated with a cumulative CRC risk of about 80% by age 70, whereas monoallelic MUTYH mutation-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 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 mutations, and screening for mutations 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 mutations may be considered for the following types of 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 D analysis for specific variants. Genetic testing or D analysis (gene sequencing, deletion and duplication testing) for the MMR genes involves assessment for MLH1, MSH2, MSH6, and PMS2 variants. The following are 3 testing strategies.

- Microsatellite instability (MSI) testing (phenotype): Individuals with high MSI either proceed to genetic testing for MLH1, MSH2, MSH6, and PMS2 or to immunohistochemical (IHC) testing.
• IHC testing (phenotype): Individuals with negative staining would proceed to genetic testing for MLH1, MSH2, MSH6, and PMS2.

• Modification strategy: Tumor tissue of patients with negative staining for MLH1 on IHC is tested for the BRAF V600E variant to determine methylation status. If the BRAF variant is not detected, the individual receives MLH1 D 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 D 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”.

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. 7,8 IHC screening has sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for each.

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

Genetic testing for an MMR gene variant is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2. The BRAF gene is often mutated in CRC when a particular BRAF variant (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present; to date, no MLH1 gene variants have been reported.

Recently, novel deletions have been reported to affect the expression of the MSH2 gene in the absence of an MSH2 gene variant, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule, are responsible. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high and/or IHC shows a lack of MSH2 expression, but no MSH2 variant is found by sequencing. EPCAM is found just upstream, in a transcriptional sense, of MSH2. Deletions of EPCAM that encompass the last 2 exons of the EPCAM gene, including the polyadenylation signal that normally ends transcription of D into messenger R, results in transcriptional “read-through” and subsequent hypermethylation of the nearby and downstream MSH2 promoter. This
hypermethylation prevents normal MSH2 protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an MSH2 variant prevents MSH2 gene expression. Several studies have characterized such EPCAM deletions, established their correlation with the presence of EPCAM-MSH2 fusion messenger Rs (apparently nonfunctional) and with the presence of MSH2 promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM variants with Lynch-like disease in families.

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

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

**Population Selection**

Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR variants, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria (low sensitivity but high specificity), Revised Bethesda guidelines (better sensitivity but poorer specificity), and risk prediction models (eg, MMRpro; PREMM; MMRpredict). While family history is an important risk factor and should not be discounted in counseling families, it has poor sensitivity and specificity for identifying Lynch syndrome. Based on this and other evidence, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing all newly diagnosed 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.

**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. 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. The estimated lifetime risk of gastrointestinal cancer ranges from 38% to 66%. Lifetime cancer risk stratified by organ site is colon and rectum (39%), stomach (29%), small bowel (13%), and pancreas (11%-36%).

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. 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 under-treatment.

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. Detection rates are higher in classic polyposis (88%) than in non-classical 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) 37 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>
</table>
| 1     | Bjork et al (2000) 54       | Observational: 195 confirmed cases of FAP underwent ileorectal anastomosis and followed for, on average, 14 y
         |                               | Cumulative risk of rectal cancer 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 |
| 2     | Järvinen (1992) 55          | Observational: 251 individuals from 81 affected families; 76 individuals diagnosed during family screening vs 116 symptomatic individuals with probands
         |                               | 65.5% of symptomatic cases had CRC vs 6.6% cases among those screened during family screening |
| 3     | Vasen et al (1990) 56       | Observational: CRC rate compared in 230 confirmed FAP cases; 104 symptomatic and 126 at-risk family members identified by screening
         |                               | 47% of symptomatic cases had CRC at a mean age of 35 y vs 4% at 24 y |

CRC: colorectal cancer; FAP: familial adenomatous polyposis.

**Section Summary: Clinically Useful**

Direct evidence of clinical utility for genetic testing of attenuated FAP is not available. Genetic testing of at-risk relatives of patients with FAP and/or a known APC variant or those requiring a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy.
**Lynch Syndrome and CRC Genetic Testing**

**Clinical Context and Test Purpose**

The purpose of genetic testing for Lynch syndrome is to:

- Detect Lynch syndrome in patients diagnosed with colorectal or endometrial cancer
- Identify at-risk relatives of patients with a diagnosed Lynch syndrome and/or a known mismatch repair (MMR) variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria
- Make a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome.

The questions addressed in this evidence review are:

1. Is there evidence that genetic testing for Lynch syndrome has clinical validity?
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 under-treatment.

**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), 57 a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009). Based on the Agency for Healthcare Research and Quality report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for MMR variants in patients already diagnosed with CRC:

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

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

Table 2. Diagnostic Results of the Different Screening Approaches
However, the diagnostic yield differences between the screening approaches were small, and the false-positive yield was with universal screening. In the selective strategy, fewer patients required tumor MMR testing and fewer required analyses of MMR variants, resulting in a rate of missed Lynch syndrome cases.

Several studies have characterized EPCAM deletions, established their correlation with the presence of EPCAM-MSH2 fusion messenger Rs (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. 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.

Bouzourene et al (2010) analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC and 16 patients with Lynch syndrome. A BRAF variant was not found in any of the Lynch syndrome patients. MLH1 promoter methylation was only present in 1 Lynch syndrome patient. However, 8 of the 11 sporadic CRC patients had the BRAF variant, and all 11 patients were MLH1 methylated, suggesting patients with BRAF variants could be excluded from germline testing for Lynch syndrome. Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients. MLH1 and PMS2 protein stains were absent in 65 patients who were subsequently tested for BRAF variant. Thirty-six (55%) of the 65 patients had the BRAF V600E variant, thus eliminating the need for further genetic testing or counseling for Lynch syndrome. Capper et al (2013) reported on a technique of V600E IHC testing for BRAF variants on a series of 91 stratified as high MSI CRC patients. The authors detected BRAF-mutated CRC with 100% sensitivity and specificity. V600E positive lesions were detected in 21% of MLH1-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore, V600E IHC testing for BRAF could be an alternative to MLH1 promoter methylation analysis. To summarize, BRAF V600E variant or MLH1 promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH1 protein expression. The presence of BRAF V600E or absence of MLH1 protein expression due to MLH1 promoter methylation rarely occurs in Lynch syndrome and would eliminate the need for further germline variant analysis for a Lynch syndrome diagnosis.

The risk of endometrial cancer in MMR variant carriers has been estimated at 34% (95% CI, 17% to 60%) by age 70, and at 8% for ovarian cancer (95% CI, 2% to 39%) by age 70. Risks do not appear to appreciably increase until after age 40. In a prospective study by Leenen et al (2012), 179 consecutive endometrial cancer patients 70 years of age or younger were analyzed for MSI, using IHC for expression of 4 MMR proteins, MMR gene methylation status, and BRAF variants. Results are presented in Table 3; 92% of patients were older than 50 years of age.

<table>
<thead>
<tr>
<th>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 99.0)</td>
<td>95.5 (95 CI, 94.7 to 96.1)</td>
<td>2.1 (95 CI, 1.6 to 2.6)</td>
</tr>
</tbody>
</table>

Cl: confidence interval.

Table 3. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome
Outcomes | N | Percent (95% Confidence Interval)
--- | --- | ---
Microsatellite stable and normal protein staining | 137 | 76
MSI-H and MLH1 absent | 32 |
Sporadic MSI-H | 31 | 17 (13 to 24)
Likely to have Lynch syndrome | 11 | 6 (3 to 11)
Variant-positive | 7 |
No variant found | 3 |
Refused further D testing | 1 |

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.

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.

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**

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).

Subtotal colectomy is recommended as an alternative to segmental resection but has not been shown superior in follow-up studies.

Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.

Surveillance and prevention for other Lynch syndrome cancers: While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In a retrospective study by Schmeler et al (2006), 315 women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and developed ovarian cancer.

In a study by Bouzourene et al (2010), surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown. Transvaginal ultrasound is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, transvaginal ultrasound in conjunction with endometrial biopsy has been recommended for surveillance.

Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supporting evidence.

In early documentation of the natural history of CRC in highly selected families with a strong history of hereditary CRC, Fitzgibbons et al (1987) indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, in those with CRC. As a result, the Cancer Genetic Studies Consortium (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. Based on this work, the 2006 joint American Society of Clinical Oncology and Society of Surgical Oncology review assessing risk-reducing surgery in hereditary cancers recommended offering both options to patients with Lynch syndrome and CRC, especially those who are younger. The societies’ review also recommended offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch anal anastomosis.
or anterior proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yurgelun et al (2012) 79</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) 80</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) 81</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) 82</td>
<td>Prospective observational; 554 individuals from 290 at-risk families with HNPC 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) 83</td>
<td>Observational; 857 at-risk individuals from 114 HNPC- 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) 84</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>
<tr>
<td>Järvinen et al (1995) 85; Järvinen et al (2000) 86</td>
<td>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.</td>
<td>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)</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; HNPC: 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>
<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>539</td>
<td>2582</td>
<td></td>
</tr>
<tr>
<td>Age &lt;50 y, and at least 1 FDR (Lynch-associated cancer)</td>
<td>530</td>
<td>2470</td>
<td></td>
</tr>
<tr>
<td>IHC triage &lt;age 50 y</td>
<td>6285</td>
<td>2442</td>
<td></td>
</tr>
<tr>
<td>IHC triage &lt;age 60 y</td>
<td>16,226</td>
<td>2450</td>
<td></td>
</tr>
<tr>
<td>IHC triage at any age; at least 1 FDR with Lynch-associated cancer</td>
<td>5786</td>
<td>2442</td>
<td></td>
</tr>
<tr>
<td>IHC triage all endometrial cancers</td>
<td>45,000</td>
<td>2413</td>
<td></td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; FDR: first-degree relative; IHC: immunohistochemical; : 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. 88 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. 89 An alternative to prophylactic surgery is surveillance for endometrial cancer using transvaginal ultrasound and endometrial biopsy. Evidence has suggested that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet has indicated surveillance reduces mortality due to endometrial cancer. Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.

Section Summary: Clinically Useful

Direct evidence of clinical utility for genetic testing for Lynch syndrome is not available. Multiple studies have demonstrated clinical utility in testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those
who followed and did not follow recommended colonic surveillance. A positive genetic test for an
MMR gene variant can also lead to changes in the management of other Lynch syndrome
malignancies.

**Genetic Testing for Juvenile polyposis syndrome and Peutz-Jeghers syndrome:**
**Clinical Context and Test Purpose**
The purpose of genetic testing for 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.

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

**Interventions**
The relevant intervention is genetic testing for SMAD4 and BMPR1 (for JPS) and ASATK11 (for PJS).
Commercial testing is available from numerous companies.

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

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

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

**Timing**
Genetic testing for SMAD4 and BMPR1 (for JPS) and ASATK11 (for PJS) may be performed at any
point during a lifetime. The necessity for genetic testing is guided by the availability of information
that alters the risk of an individual of having or developing JPS and PJS.

**Setting**
Ordering and interpreting genetic testing may be complex and is best done by experienced
specialists such as gastroenterologists. Most patients are likely to be tested in an outpatient setting.
Referral for genetic counseling is important for the explanation of genetic disease, heritability,
genetic risk, test performance, and possible outcomes.
Study Selection Criteria
For the evaluation of clinical validity of the genetic test, studies that met the following eligibility criterion were considered:

Reported on the diagnostic yield of the test.

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

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

Table 6. 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) 92</td>
<td>Observational; 17 clinically diagnosed children with PJS</td>
<td>STK11 variants detected in 29.4% (5/17)</td>
</tr>
<tr>
<td>Calva-Cerqueira et al (2009) 93</td>
<td>Observational; 102 unrelated JPS probands analyzed all of whom met clinical criteria for JPS</td>
<td>SMAD4 and BMPR1A variants detected in 41% (42/102) JPS probands</td>
</tr>
<tr>
<td>Aretz et al (2007) 94</td>
<td>Observational; 80 unrelated patients (65 met clinical criteria for typical JPS; 15 presumed to have JPS) were examined by direct sequencing for SMAD4, BMPR1A, and PTEN variants</td>
<td>SMAD4 and BMPR1A variants detected in 60% of typical JPS patients and none in presumed JPS patients; overall diagnostic yield, 49%</td>
</tr>
<tr>
<td>Volikos et al (2006) 95</td>
<td>Observational; 76 clinically diagnosed with PJS</td>
<td>Detection rate of germline variants was about 80% (59/76)</td>
</tr>
<tr>
<td>Aretz et al (2005) 96</td>
<td>Observational; 71 patients (56 met clinical criteria for PJS; 12 presumed to have PJS)</td>
<td>STK11 variant detected in 52% (37/71)</td>
</tr>
</tbody>
</table>

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

Section Summary: Clinically Valid
The likelihood of detecting a pathogenic variant is highly dependent on the presence of clinical features and family history. Detection rates for JPS and PJS have been reported to be between 60% and 41% and 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. 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) 97</td>
<td>Observational: 35 patients had germline variants in BMPR1A (8 patients) or SMAD4 (27) with a median follow-up of 11 y</td>
<td>No patient was diagnosed with cancer in the BMPR1A group, whereas 4 men with a SMAD4 variant developed GI (n=3) or extraintestinal (n=1) cancer. The GI cancer risk in patients with JPS and a SMAD4 variant was 11% (3/27).</td>
</tr>
<tr>
<td>Resta et al (2013) 98</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) 36</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) 99</td>
<td>Observational: 31 patients with PJS; STK11 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) 29</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

National Comprehensive Cancer Network (NCCN) guidelines (v. are summarized in Table 8.31

Table 8. Criteria for Evaluation of Lynch Syndrome

Known LS variant in the family

An individual with colorectal or endometrial cancer and any of the following: Diagnosed <50 y.

Another synchronous or metachronous LS-related cancer ≥1 first-degree or second-degree relative with LS-related cancer diagnosed <50 y ≥2 first-degree or second-degree relatives with LS-related cancers regardless of age.

An individual with colorectal or endometrial cancer at any age with tumor showing evidence of MMR deficiency, either by MSI or loss of MMR protein expression

Family history of any of the following: ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 y ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer ≥2 first-degree or second-degree relatives with LS-related cancer, ≥1 diagnosed <50 y ≥3 first-degree or second-degree relatives with LS-related cancers, a regardless of age

An individual with a LS-related cancer or unaffected individual with ≥5% riskc of having an MMR gene variant based on predictive models (PREMM5, MMRpro, MMRpredict)

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

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

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

c There are recent data that resulted in a lower threshold of ≥2 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 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. recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years. 100 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. 101 and for CRC screening (v. 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. . 83 NCCN guidelines on genetic/familial high-risk assessment for colorectal indicate for MLH1, MSH2, and EPCAM variant carriers that surveillance with colonoscopy should begin “at age 20 to 25 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years. 31 “MSH6 variant carriers should begin surveillance with colonoscopy at age 30 to 35 years, and PMS2 carriers should begin surveillance at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 years for MSH6 and PMS2 variant carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years. “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. 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.

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.

### 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 annuallyClinical breast exam every 6 mo</td>
<td>25 y</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 cord/Sertoli cell tumors) Cervix (typically cervical adenoma malignum) Uterus</td>
<td>18-21/109</td>
<td>Pelvic examination and Pap smear annuallyConsider transvaginal ultrasound</td>
<td>18 to 20 y</td>
</tr>
<tr>
<td>Testes (typically sex cord/Sertoli cell tumors)</td>
<td></td>
<td>Annual testicular exam and observation for feminizing changes</td>
<td>10 y</td>
</tr>
<tr>
<td>Lung</td>
<td>15-17</td>
<td>Provide education about symptoms and smoking cessationNo other specific recommendations have been made</td>
<td></td>
</tr>
</tbody>
</table>

CT: computed tomography; MRI: magnetic resonance imaging.

### Table 10. Risk and Surveillance Guidelines for Juvenile Polyposis 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>Colon</td>
<td>40-50</td>
<td>Colonoscopy every year if polyps are found and every 2-3 y if no polyps are found</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</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.
a In families without an identified genetic variants, 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.

**American College of Gastroenterology**
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.

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 D 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 (eg, MSH2, MSH6, EPCAM, PMS2, or MLH1).

Full germline genetic testing for Lynch syndrome should include D 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.

Preventive Services Task Force Recommendations
No Preventive Services Task Force recommendations for genetic testing of Lynch syndrome and other inherited colon cancer syndromes have been identified.

Medicare National Coverage
Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (ie, clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. The Centers for Medicare & Medicaid Services recognizes Lynch syndrome as “an autosomal dominant syndrome that accounts for about 3% to 5% of colorectal cancer cases. [Lynch] syndrome variants occur in the following genes: hMLH1, hMSH2, hMSH6, PMS2, and EPCAM. The Centers for Medicare & Medicaid Services also recognize 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>
</thead>
<tbody>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01646112</td>
<td>Living in Lynch Syndrome Limbo: Exploring the Meaning of Uncertain Genetic Test Results</td>
<td>34</td>
<td>Feb 2016 (completed)</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.

VII. **Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. **References**


