DRAFT

BlueCross BlueShield of Alabama

Name of Policy:

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy #: 720
Category: Laboratory

Latest Review Date: October 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Genetic testing is available for both affected individuals 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, Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), MUTYH-associated polyposis, Lynch syndrome–related endometrial cancer, juvenile polyposis syndrome and Peutz-Jeghers syndrome

Hereditary Colorectal Cancers

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

FAP and Associated Variants

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

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

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

MUTYH if APC is negative for variants, and screening for variants associated with Lynch syndrome.

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

Testing

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

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

Lynch Syndrome

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

Testing

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

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

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

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

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

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

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

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

Recently, novel deletions have been reported to affect the expression of the MSH2 gene in the absence of an MSH2 gene variant, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule, are responsible. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and/or IHC shows a lack of MSH2 expression, but no MSH2 variant is found by sequencing. EPCAM is found just upstream, in a transcriptional sense, of

MSH2. Deletions of EPCAM that encompass the last 2 exons of the EPCAM gene, including the polyadenylation signal that normally ends transcription of DNA into messenger RNA, resulting in transcriptional “read-through” and subsequent hypermethylation of the nearby and downstream MSH2 promoter. This hypermethylation prevents normal MSH2 protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an *MSH2* variant prevents MSH2 gene expression. Several studies have characterized such *EPCAM* deletions, established their correlation with the presence of EPCAM-MSH2 fusion messenger RNAs (apparently nonfunctional) and with the presence of MSH2 promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM variants with Lynch-like disease in families.

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

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

Population Selection

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

- Family members of Lynch syndrome patients with a known MMR variant; family members would be tested only for the family variant; those testing positive would benefit from early and increased surveillance to prevent future CRC.
- Patients with a differential diagnosis of Lynch syndrome vs attenuated FAP vs MAP.

- For Lynch syndrome patients, genetic testing of the proband with CRC likely benefits the proband where Lynch syndrome is identified, and appropriate surveillance for associated malignancies can be initiated and maintained and benefits family members by identifying the family variant.

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

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

A clinical diagnosis of JPS is made on the basis of presence of any one of the following: at least 3 to 5 juvenile polyps in the color or multiple juvenile polyps in other parts of the gastrointestinal tract or any number of juvenile polyps in a person with a known family history of juvenile polyps. It is recommended that individuals who meet clinical criteria for JPS should undergo genetic testing for a germline mutation in the BMPR1A and SMAD4 genes for a confirmatory diagnosis of JPS and to counsel at-risk family members.

Peutz-Jeghers Syndrome
It 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 cancer. It is a rare disorder with an estimated incidence of 1 in 8000 to 200,000. In most cases, 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 mutations. Variant in STK11 are 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 colorectal, 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 colorectal (39%), stomach (29%), small bowel (13%), and pancreas (11 to 36%).

A clinical diagnosis of PJS is made on the basis if an individual meets 2 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, or fingers or family history of PJS. Individuals who meet clinical criteria for PJS should undergo genetic testing for a germline mutation in the STK11 gene for a confirmatory diagnosis of PJS and to counsel at-risk family members. In addition, if there is a known SMAD4 variant in the family, genetic testing should be performed within the first 6 months of life due to hereditary hemorrhagic telangiectasia risk.

Policy:

Effective for dates of service on or after October 1, 2018:

APC Testing

Genetic testing for APC gene variants **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the following patients:

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

Genetic testing is available and appropriate for the I1307K mutation in the APC gene in those individuals that meet either the Revised Amsterdam criteria **or** the Revised Bethesda criteria **and** are of Ashkenazi Jewish decent (see policy guidelines section for criteria)

Genetic testing for APC gene variants **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

MUTYH Testing

Genetic testing for MUTYH gene variants **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage following patients:

- Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome and a negative result for APC gene variants. A family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

MAP Testing

Genetic testing for the MUTYH-associated polyposis (MAP) for colorectal cancer (targeted mutation analysis for the two most common variants Y165C and G382D, followed by sequencing if negative) **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage when at least **ONE** of the following criteria are met:

- Patients with multiple adenomas or polyps (>10); **OR**

- Patients in whom FAP or attenuated atypical FAP is suspected but APC genetic testing has been reported as negative for a disease-causing mutation.

IHC or MSI testing
Either the Immunohistochemistry (IHC) test **OR** the Microsatellite instability (MSI) test to identify those at risk for carrying a Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer (HNPCC)) gene mutation and/or genetic testing to determine carrier status of the Lynch Syndrome (HNPCC) gene **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage who meet **either** the Amsterdam II clinical criteria **or** Bethesda criteria (see policy guidelines section for criteria).

MMR Gene Testing
Genetic testing for MMR genes (MLH1, MSH2, MSH6, PMS2) **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the following patients:

- Patients with colorectal cancer (CRC), for the diagnosis of Lynch syndrome
- Patients with endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, for the diagnosis of Lynch syndrome.
- At-risk relatives of patients with Lynch syndrome with a known MMR gene variant.
- Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. Whether testing begins with APC variants or screening for MMR genes depends on clinical presentation.
- Patients without CRC but with a family history meeting the Amsterdam II clinical criteria or Revised Bethesda criteria, when no affected family members have been tested for MMR variants.
- Clinical genetic testing for individuals meeting the Amsterdam II clinical criteria or Revised Bethesda criteria can include testing for mutations in any of the MMR genes (MLH1, MSH2, MSH6, PMS2).

EPCAM Testing
Genetic testing for EPCAM gene variants **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage when any one of the following 3 major criteria (solid bullets) is met:

- Patients with CRC, for the diagnosis of Lynch syndrome when:
  - Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for a MSH2 germline variant; **OR**
  - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in MSH2, MLH1, PMS2, and MSH6; **OR**
- At-risk relatives of patients with Lynch syndrome with a known EPCAM variant; **OR**
- Patients without CRC but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR variants, and when sequencing for MMR variants is negative.

BRAF V600E or MLH1 Promoter Methylation
Genetic testing for BRAF V600E **or** MLH1 promoter methylation **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage to exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a CRC tumor on immunohistochemical (IHC) analysis.

SMAD4 and BMPR1A Testing
Genetic testing for SMAD4 and BMPR1A gene variants **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage when any one of the following major criteria (solid bullets) is met:

- Individual has a clinical diagnosis of juvenile polyposis syndrome based on the presence of any 1 of the following:
  - at least 3 to 5 juvenile polyps in the colon
  - multiple juvenile polyps in other parts of the gastrointestinal tract
  - any number of juvenile polyps in a person with a known family history of juvenile polyps.
- Individual is an at-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome.

STK11 Testing
Genetic testing for STK11 gene variants **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage when any one of the following major criteria (solid bullets) is met:

- Individual has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any two of the following:
  - presence of two or more histologically confirmed Peutz-Jeghers polyps of the small intestine
  - characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - family history of Peutz-Jeghers syndrome
- Individual is an at-risk relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome or STK11 gene mutation
- Any individual with a diagnosis of small bowel hamartomatous polyposis and who demonstrates hyperpigmentation of the digits and mucosa of the external genitalia

Carrier Status testing
Genetic testing to determine the carrier status of the Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer (HNPCC)) gene **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage in individuals without a personal history of HNPCC but have a first- or second- degree relative with documented HNPCC gene mutation.

Genetic testing for all other gene variants for Lynch syndrome or CRC does **not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Policy Guidelines

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

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

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

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

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

Testing At-Risk Relatives

Due to the high lifetime risk of cancer of most genetic syndromes discussed in this policy, "at-risk relatives" primarily refers to first-degree relatives. However, some judgment must be allowed, e.g., in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.

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.

Effective for dates of service August 1, 2003 through September 31, 2018:
Genetic testing for inherited susceptibility of **Colon Cancer meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage per diagnosis when the following criteria are met:

Genetic testing for adenosis polyposis coli gene (APC) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following:

- First degree relatives of patients with **familial adenomatous polyposis (FAP)** and/or a known APC mutation;
- Patients with a differential diagnosis of attenuated FAP vs MYH-associated polyposis vs Hereditary Nonpolyposis Colorectal Cancer (HNPCC) also known as Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends on clinical presentation.

Genetic testing for APC gene mutations does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for colorectal cancer patients with classical FAP.

Genetic testing for MYH gene mutations meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the following patients:

- Patients with a differential diagnosis of attenuated FAP vs MYH-associated polyposis vs Lynch syndrome/HNPCC and a negative result for APC gene mutations. Family history of no parents or children with FAP is consistent with MYH-associated polyposis (autosomal recessive).

Genetic testing for the MYH-associated polyposis (MAP) for colorectal cancer (targeted mutation analysis for the two most common variants Y165C and G382D, followed by sequencing if negative) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage when at least **ONE** of the following criteria are met:

- Patients with multiple adenomas or polyps (>10); **OR**
- Patients in whom FAP or attenuated atypical FAP is suspected but APC genetic testing has been reported as negative for a disease-causing mutation.

Genetic testing for MMR gene mutations meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the following patients:

- Patients with colorectal cancer, for the diagnosis of Lynch syndrome/HNPCC;

- First or second degree relatives of patients with Lynch syndrome with a known MMR mutation;
- Patients with a differential diagnosis of attenuated FAP vs. MYH-associated polyposis vs. Lynch syndrome/HNPCC. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation;
- Patients without colorectal cancer but with a family history meeting the **Revised Amsterdam or Revised Bethesda criteria,** when no affected family members have been tested for MMR mutations. (See criteria below).

Revised Amsterdam criteria (must meet **all** of the following):

- Three or more relatives with a histologically verified Lynch syndrome/HNPCC related cancers, and
- One of whom is a first degree relative of the other two; and
- Two successively affected generations; and
- One or more Lynch syndrome/HNPCC related cancers diagnosed before 50 years of age.

Revised Bethesda criteria (must meet **one** of the following):

- Colorectal diagnosis is made younger than 50 years of age.
- Individual has or had a second colorectal cancer or another cancer (endometrial, stomach, pancreas, small intestine, ovary, kidney, ureters, or bile duct) that is associated with HNPCC/Lynch syndrome.
- Individual is younger than 60 years and the cancer has certain characteristics seen with HNPCC/Lynch syndrome when viewed under the microscope or with other lab tests.
- Individual has a first-degree relative younger than 50 who was diagnosed with colorectal cancer or another cancer often seen in HNPCC carriers (endometrial, stomach, pancreas, small intestine, ovary, kidney, ureter, or bile duct).
- Individual has 2 or more first- or second-degree relatives who had colorectal cancer or an HNPCC-related cancer at any age.

Clinical genetic testing is available and appropriate for the I1307K mutation in the APC gene in those individuals that meet the above criteria and are of Ashkenazi Jewish decent.
Immunohistochemistry (IHC) and Microsatellite instability (MSI) to identify those at risk for carrying an Hereditary Nonpolyposis Colorectal Cancer (HNPCC) gene mutation and/or genetic testing to determine carrier status of the HNPCC gene meets Blue Cross and Blue Shield's medical criteria for coverage in **patients who meet either the Amsterdam Revised <u>or</u> Bethesda** criteria:

- **Revised Amsterdam criteria** (must meet **all** of the following):
  - Three or more relatives with a histologically verified HNPCC related cancers, one of whom is a first degree relative of the other two; **and**
  - Two successively affected generations; **and**
  - One or more HNPCC related cancers diagnosed before 50 years of age.

- **Bethesda criteria** (may meet **any** of the following):
    - Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers, (biliary, endometrial, urinary or ovarian); **OR**
    - Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at less than 45 years of age and adenoma diagnosed at less than 40 years of age; **OR**
    - Individuals with colorectal cancer or endometrial cancer with an undifferentiated pattern on histopathology diagnosed at less than 45 years of age; **OR**
    - Individuals with signet ring cell type colorectal cancer diagnosed at less than 45 years or age; **OR**
    - Individuals with adenomas diagnosed at less than 40 years of age.

Clinical genetic testing for individuals meeting these criteria can include testing for mutations in any of the following genes: PMS2, MLH1, MSH2, and MSH6.

Genetic testing to determine the carrier status of the Hereditary Nonpolyposis Colorectal Cancer (HNPCC) gene meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **individuals without a personal history of HNPCC** but have a **first- or second-degree relative with documented HNPCC gene mutation**.

Peutz-Jeghers Syndrome
Genetic testing for the STK11 gene mutations meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following patients:

- Any individual with a diagnosis of small bowel hamartomatous polyposis and who demonstrates hyperpigmentation of the digits and mucosa of the external genitalia; OR
- Unaffected individuals who have a family history of a documented STK11 gene mutation in a first or second degree relative.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

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 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 MUTYH-associated polyposis (MAP) vs Lynch syndrome.

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

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

Patients

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

Interventions

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

Comparators

The following practice is currently being used to make decisions about managing FAP and MUTYH- associated polyposis: no genetic testing.

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

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

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

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

Study Selection Criteria
For the evaluation of clinical validity of the genetic test, studies that meet the following eligibility criteria 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 originally informed by a TEC Assessment (1998). The additional information on attenuated FAP and on MAP diagnostic criteria and genetic testing is based on information from GeneReviews and from several publications that build on prior, cited research.

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

test (Y165C, G382D) and 98% of pathogenic MUTYH variants are detected by full gene sequencing.

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

Section Summary: Clinically Valid

The analytic and clinical sensitivity and specificity for APC and MUTYH were 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%).

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 randomized controlled trials (RCTs).

No RCTs were identified assessing the clinical utility of genetic testing for FAP and MUTYH-associated polyposis.

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 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 intensified screening program resulting in psychological relief.

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.

A TEC Assessment (1998) offered the following conclusions:

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

Studies summarizing clinical utility for genetic testing for FAP are summarized in Table 1.

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

Author	Study Design and Population	Results
Vasen et al (1990)	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
Bjork et al (2000)	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
Järvinen (1992)	Observational: 251 individuals from 81 affected families; 76 individuals diagnosed during family screening compared with 116 symptomatic individuals with probands	65.5 % of symptomatic cases had CRC vs 6.6% cases among those screened during family screening

CRC: colorectal cancer; FAP: familial adenomatous polyposis.

Section Summary: Clinically Useful

Direct evidence of clinical utility for genetic testing of 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

which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.

Lynch Syndrome and Colorectal Cancer Genetic Testing

Clinical Context and Test Purpose

The purpose of genetic testing for Lynch syndrome is to:

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

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

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

Patients

The relevant population of interest is 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 MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes. Commercial testing is available from numerous companies.

Comparators

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

Outcomes

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

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

Timing

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

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

Study Selection Criteria
For the evaluation of clinical validity of the genetic test, studies that meet the following eligibility criteria 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 published by the Agency for Healthcare Research and Quality (2007), a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009), and an EGAPP recommendation (2009) for genetic testing in CRC. Based on the Agency for Healthcare Research and Quality report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for MMR variants in patients already diagnosed with CRC:

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

Moreira et al (2012) reported the comparison of universal testing of CRC patients with alternative screening approaches.59 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 10,206 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), with a sensitivity of 100% (95% confidence interval [CI], 99.3% to 100%), specificity of 93% (95% CI, 92.0% to 93.7%), and diagnostic yield of 2.2% (95% CI, 1.7% to 2.7%).
- The Bethesda guidelines screening sensitivity was 87.8% (95% CI, 78.9% to 93.2%), with a specificity of 97.5% (95% CI, 96.9% to 98.0%) and a diagnostic yield of 2.0% (95% CI, 1.5% to 2.4%; p<0.001).
- The screening sensitivity with the Jerusalem recommendations was 85.4% (95% CI, 77.1% to 93.6%), with a specificity of 96.7% (95% CI, 96.0% to 97.2%) and a diagnostic yield of 1.9% (95% CI, 1.4% to 2.3%; p<0.001).
- The selective strategy had a sensitivity of 95.1% (95% CI, 89.8% to 99.0%), with a specificity of 95.5% (95% CI, 94.7% to 96.1%) and a diagnostic yield of 2.1% (95% CI, 1.6% to 2.6%; p<0.001).

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

Several studies have characterized EPCAM deletions, established their correlation with the presence of *EPCAM-MSH2* fusion messenger RNAs (apparently nonfunctional) and with the presence of *MSH2* promoter hypermethylation, and, most importantly, have shown the cosegregation of these *EPCAM* variants with Lynch-like disease in families. Because studies differ slightly in how patients were selected, the prevalence of these EPCAM variants is difficult to estimate but may be in the range of 20% to 40% of patients/families who meet Lynch syndrome criteria, do not have an MMR variant, but have MSI-high tumor tissue. Kempers et al (2011) reported that carriers of an *EPCAM* deletion had a 75% (95% CI, 65% to 85%) cumulative risk of CRC by age 70 years, which did not differ significantly from that of carriers of an *MSH2* deletion (77%; 95% CI, 64% to 90%); mean age at diagnosis was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0% to 27%) by age 70 compared with carriers of an MSH2 variant (51%; 95% CI, 33% to 69%; p<0.001).

Bouzourene et al (2010) analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC and 16 patients with Lynch syndrome. BRAF variant was not found in any of the Lynch syndrome patients. MLH1 promoter methylation was only present in 1 Lynch syndrome patient. However, 8 of the 11 sporadic CRC patients had the BRAF variant, and all 11 patients were MLH1 methylated, suggesting patients with BRAF variants could be excluded from germline testing for Lynch syndrome. Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients. MLH1 and PMS2 protein stains were absent in 65 patients who were subsequently

tested for BRAF variant. Thirty-six (55%) of the 65 patients had the BRAF V600E variant, thus eliminating the need for further genetic testing or counseling for Lynch syndrome. Capper et al (2013) reported on a technique of V600E IHC testing for BRAF variants on a series of 91 stratified as high MSI CRC patients. The authors detected BRAF-mutated CRC with 100% sensitivity and 98.8% specificity. V600E positive lesions were detected in 21% of MLH1-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore, V600E IHC testing for BRAF could be an alternative to MLH1 promoter methylation analysis. To summarize, BRAF V600E variant or MLH1 promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH 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 2012 prospective study, 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 2; 92% of patients were older than 50 years of age.

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 2012 prospective study, 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 2; 92% of patients were older than 50 years of age.

Table 2. 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	
Refuses further DNA testing	1	

H: high; MSI: 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 randomized controlled trials.

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 preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis or segmental colectomy).

Genetic testing of at-risk relatives of patients with Lynch syndrome and/or a known MMR variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria or risk prediction scores has clinical utility:

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

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

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

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

1. The chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant.
2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. About half of relatives received counseling, and 95% of these 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, prevention for other Lynch syndrome cancers.

3. The chain of evidence from descriptive studies and expert opinion is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., cancer index patient).
4. Subtotal colectomy is recommended as an alternative to segmental resection but has not been shown superior in follow-up studies.
5. 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, 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 (2006), of 315 women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.
   - In a 2010 study, surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown.10 Transvaginal ultrasound (TVUS) is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, TVUS 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 supportive evidence.

Early documentation (1987) of the natural history of CRC in highly selected families with a strong history of hereditary CRC indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, in those with CRC. As a result, in 1997, the Cancer Genetic Studies Consortium recommended that if CRC is diagnosed in patients with an identified variant or a strong family history, a subtotal colectomy with ileorectal anastomosis should be considered as an option to segmental resection. Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. One 2003 study suggested that subtotal colectomy with ileorectal anastomosis markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance. A 2003 mathematical model comparing total colectomy plus ileorectal anastomosis with hemicolectomy estimated increased life expectancies of 2.3, 1, and 0.3 years for ages 27, 47, and 67, respectively; for stage I cancer, estimated life expectancies for the same ages were 3.4, 1.5, and 0.4, respectively. Based on this work, the 2006 joint American Society of Clinical Oncology and Society of Surgical Oncology review assessing risk-reducing surgery in hereditary cancers recommended offering both options to patients with Lynch syndrome and CRC, especially those who are younger. The societies' review also recommended offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch anal anastomosis or anterior

proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

Studies summarizing the clinical utility for genetic testing for Lynch syndrome are summarized in Table 3.

Table 3. Summary of Clinical Validity Studies for Genetic Testing for Lynch Syndrome

Study	Study Design and Population	Results
Järvinen et al (1995) (2000)	Observational; 252 at-risk individuals from 20 of 22 families with MMR variants invited for colonoscopy screening every 3 y; 133 agreed; 118 declined. Of those who declined, 8 (15%) had screening examinations outside of the study.	--Screening vs nonscreening --Incidence of CRC: 4.5% (n=6) vs 11.9% (n=14) (p=0.03) --6 vs 12 deaths within 10 y (p=0.08)
De Vos tot Nederveen Cappel et al (2002)	Observational; 857 at-risk individuals from 114 HNPCC- or MMR-positive families.	10-y cumulative risk of CRC, 15.7% vs 3.4% for partial vs subtotal colectomy
Dove-Edwin et al (2005)	Prospective observational; 554 individuals from 290 at-risk families with HNPCC or MMR variants followed for 16 y	Estimated 72% decrease in CRC death in screened individuals
Järvinen et al (2009)	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	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
Syngal et al (1998)	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	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.
Engel et al (2010)	Prospective cohort: Assessed efficacy of annual colonoscopic surveillance in 1126 at-risk individuals from families with LS	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.
Yurgelun et al (2012)	--Prospective cohort: Examined uptake of risk-	--In cross-sectional cohort, 58/77 (75%) women

	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	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.

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

Kwon et al (2011) developed a Markov Monte Carlo simulation model to compare 6 strategies for Lynch syndrome testing in women with endometrial cancer.87 Overall, the results suggested that IHC triage of women at any age who have at least 1 first-degree relative with a Lynch-associated cancer was the most cost-effective strategy (incremental cost-effectiveness ratio, $9126) 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 4.

Table 4. Modeling of Endometrial Cancer Screening Strategies for Detecting Lynch Syndrome

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

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

Female patients with Lynch syndrome who choose risk-reducing surgery are encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. As noted, in a retrospective study by Schmeler et al (2006), women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer. In another retrospective cohort study (2010), hysterectomy improved survival among female colon cancer survivors with Lynch

syndrome. This study also estimated that, for every 100 women diagnosed with Lynch syndrome–associated CRC, about 23 will 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) found 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 the MMR variant. This might support a clinical management scenario rather than prophylactic surgery. An alternative to prophylactic surgery is surveillance for endometrial cancer using TVUS and endometrial biopsy. Evidence has indicated that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet indicates 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 1 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:

- Make a confirmatory diagnosis of JPS or PJS in patients suspected of these disorders based on clinical features
- 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 population of interest is patients suspected of JPS or PJS or individuals who are at-risk relatives of patients suspected of or diagnosed with a polyposis syndrome 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 (e.g., cancer screening, surgical intervention including polyp resection, gastrectomy, colectomy) to prolong life.

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

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

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

Study Selection Criteria
For the evaluation of clinical validity of the genetic test, studies that meet the following eligibility criteria 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).

Studies summarizing the clinical utility for genetic testing for JPS and PJS are summarized in Table 5.

Table 5. Summary of Clinical Validity Studies Assessing Genetic Testing for JPS and PJS.

Study	Study Design and Population	Results
Yang and Seo (2010)	Observational; 17 clinically diagnosed children with PJS	--*STK11* variants detected in 29.4% (5/17)
Calva-Cerqueira (2009)	Observational; 102 unrelated JPS probands analyzed all of whom met clinical criteria for JPS	---*SMAD4* and *BMPR1A* variants identified in 41% (42/102) JPS probands
Aretz et al (2007)	Observational; 80 unrelated patients (65 met clinical criteria for typical JPS; 15 presumed to have JPS) were examined by direct sequencing of *SMAD4*, *BMPR1A*, and *PTEN* variant	*SMAD4* and *BMPR1A* variants identified in 60% of typical JPS patients and none in presumed JPS patients yielding an overall diagnostic yield of 49%
Volikos et al (2006)	Observational; 76 clinically diagnosed with PJS	Detection rate of germline variants was about 80% (59/76)
Artez et al (2005)	Observational; 71 patients (56 met clinical criteria for PJS; 12 presumed to have PJS)	*STK11* variant detected in 52% (37/71)

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

Section Summary: Clinically Valid

The likelihood of detecting a pathogenic variant is highly dependent on the presence of clinical features and family history. Detection rates for JPS and PJS have been reported to be between 60 to 41% and 29.4% to 80%.

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 randomized controlled trials.

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 suspected with JPS and PJS has clinical utility:

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

Genetic testing of individuals who are at-risk relatives of patients suspected of or diagnosed with a 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 Peutz-Jeghers 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.

Studies summarizing clinical utility for genetic testing for JPS and Peutz-Jeghers syndrome are summarized in Table 6.

Table 6. Summary of Clinical Utility Studies for Genetic Testing for Juvenile Polyposis Syndrome and Peutz-Jeghers Syndrome

Study	Study Design and Population	Results
Aytac et al (2015)	Observational: 35 patients had germline variants in either *BMPR1A* (8 patients) or *SMAD4* (27) with a median follow-up of 11 y	No patient was diagnosed with cancer in the *BMPR1A* group, whereas 4 men with a *SMAD4* mutation developed gastrointestinal (3) or extraintestinal (1) cancer. The gastrointestinal cancer risk in patients with juvenile polyposis syndrome and a *SMAD4* variant was 11% (3/27).
Resta et al (2013)	Observational: 119 patients with Peutz-Jeghers syndrome	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.
Salloch et al (2009)	Observational: 31 patients with Peutz-Jeghers syndrome; STK11 variants in 16/22 families	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
Brosens et al	Observational: 84 patients with juvenile polyposis contributing 1652.2 person-years of follow-up vs general population of the U.S. (SEER data)	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
Lier et al (2010)	Systematic review: 21 original articles, 20 cohort studies, and 1 meta-analysis (total N=1644 Peutz-Jeghers syndrome patients)	349 patients developed 384 malignancies at an average age of 42 y. Lifetime risk for any cancer varied between 37% and 93% with RRs ranging from 9.9 to 18 in

	comparison with the general population.

CI: confidence interval; CRC: colorectal cancer; FAP: familial adenomatous polyposis; RR: relative risk.

Section Summary: Clinically Useful

Direct evidence of clinical utility for genetic testing of a JPS or PJS is not available. Genetic testing of patients suspected of 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 which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.

Summary of Evidence

For individuals who are suspected of attenuated FAP, MAP, and Lynch syndrome, or are at-risk relatives of patients with FAP who receive genetic testing for APC, 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 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 did and did not follow 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 immunohisto-chemical analysis who receive genetic testing for BRAF V600E or MLH1 promoter methylation, the evidence includes a few 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) individuals who 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, 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, BMPR1A, or STK11 variant 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 which currently unaffected at-risk family members 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.

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 were in agreement with the overall approach described in this policy.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
National Comprehensive Cancer Network (NCCN) guidelines (v.1.2018) for genetic/familial high-risk assessment of colorectal cancer (CRC) recommend 2 approaches to Lynch syndrome

variant screening: (1) all newly diagnosed CRC or (2) all CRC patients diagnosed before age 70 plus those diagnosed at ages 70 and older who meet Bethesda guidelines. Additionally, NCCN guidelines (v.2.2018) recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years.

Genetic testing is recommended for at-risk family members of patients with positive variants in MLH1, MSH2, MSH6, or 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 (IHC) analysis to exclude a diagnosis of Lynch syndrome. These guidelines also address familial adenomatous polyposis (FAP; classical and attenuated), and MUTYH-associated polyposis (MAP), consistent with the information in this evidence review.

Evaluation of Genomic Applications in Practice and Prevention recommendations noted that the current evidence is insufficient to clearly support benefit from genetic testing to the index patient with CRC if found to have Lynch syndrome. However, professional societies have reviewed the evidence and concluded that genetic testing likely has direct benefits for at least some patients with CRC and Lynch syndrome by differing recommendations for postsurgical surveillance, and for those who choose prophylactic surgical treatment instead of surveillance. NCCN guidelines for colon cancer (v.3.2018) and for CRC screening (v.3.2018) 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. 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." "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. 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 regarding the efficacy of various screening modalities in juvenile polyposis syndrome and Peutz-Jeghers syndrome. NCCN cancer risk and surveillance guidelines for these 2 indications are summarized in Tables 7 and 8.

Table 7. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome (Category 2A Recommendations)

Site	Lifetime Risk, %	Screening Procedure and Interval	Initiation Age, y
Breast	45-50	--Mammogram and breast MRI annually --Clinical breast exam every 6 mo	~25y
Colon	39	Colonoscopy every 2-3 y	Late teens
Stomach	29	Upper endoscopy every 2-3 y	Late teens
Small intestine	13	Small bowel visualization (CT or MRI enterography or video capsule endoscopy baseline at 8-10 y with follow-up interval based on findings but at least by age 18, then every 2-3 y, though this may be individualized, or with symptoms)	~8 to 10 y
Pancreas	11-36	Magnetic resonance cholangiopancreatography with contrast or endoscopic ultrasound every 1-2 h	~30-35 y
Ovary (typically benign sex cord/Sertoli cell tumors)	18-21	--Pelvic examination and Pap smear annually --Consider transvaginal ultrasound	~18-20 y
Cervix (typically cervical adenoma malignum)	10	--Pelvic examination and Pap smear annually --Consider transvaginal ultrasound	~18-20 y
Uterus	9	--Pelvic examination and Pap smear annually --Consider transvaginal ultrasound	~18-20 y
Testes (typically sex cord/Sertoli cell tumors)		Annual testicular exam and observation for feminizing changes	~10 y
Lung	15-17	Provide education about symptoms and smoking cessation No other specific recommendations have been made	

CT: computed tomography; MRI: magnetic resonance imaging**.**

Table 8. Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome (Category 2A Recommendations)

Site	Lifetime Risk, %	Screening Procedure and Interval	Initiation Age, y
Colon	40-50	Colonoscopy every year if polyps are found and every 2-3 y if no polyps are found	~15 y
Stomach	21 if multiple polyps	Upper endoscopy annually	~15 y

		if polyps are found and every 2-3 y if no polyps are found[a]	
Small intestine	Rare, undefined	No recommendations have been made	
Pancreas	Rare, undefined	No recommendations have been made	
HHT	Undefined	In individuals with *SMAD4* variants, screen for vascular lesions associated with HHT	Within first 56 mo of age

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

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

Lynch syndrome (LS)

- "All newly diagnosed colorectal cancers should be evaluated for mismatch repair deficiency.
- "Analysis may be done by immunohistochemical (IHC) 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, 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."

Adenomatous polyposis syndromes

- "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."

Juvenile polyposis syndrome:

- "Genetic evaluation of a patient with possible juvenile polyposis syndrome should include testing for SMAD4 and BMPR1A mutations."
- "Surveillance of the 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 IRA or proctocolectomy and IPAA 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)."

Peutz-Jeghers syndrome:

- "Genetic evaluation of a patient with possible PJS 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 CT in smokers (conditional recommendation, low quality of evidence)."

American Society of Clinical Oncology and Society of Surgical Oncology

In 2015, the American Society of Clinical Oncology concluded that the European Society for Medical Oncology clinical practice guideline 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 relate to genetic testing hereditary CRC syndromes are summarized below:

- "Tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines.
- If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.
- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1).
- Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis.
- Patients with multiple colorectal adenomas should be considered for full germline genetic testing of APC and/or MUTYH.

- Germline testing of MUTYH can be initiated by screening for the most common mutations (G396D, Y179C) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered."

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

Key Words:

Genetic testing, genetic test, genetic disorder, mutation, colon cancer, colorectal cancer, Lynch Syndrome, hereditary nonpolyposis colorectal cancer, HNPCC, CRC, inherited colon cancer syndromes, hereditary colorectal cancers, familial adenomatous polyposis, FAP, adenosis polyposis coli gene, APC, Amsterdam criteria, Bethesda criteria, microsatellite instability, MSI, MYH mutation, MYH, MUTYH, MUTYH-associated polyposis, MAP, germline variants, germline alterations, MLH1, MLH1 promoter methylation, MSH2, MSH6, PMS2, MMR, IHC, immunohistochemical testing, BRAF, gene variant, Juvenile Polyposis Syndrome, BMPR1A, SMAD4, JPS, Peutz-Jeghers Syndrome, STK11, LKB1, PJS, EPCAM, genetic counseling

Approved by Governing Bodies:

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

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	; known familial variants

81203	; duplication/deletion variants
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	; full sequence analysis
81293	; known familial variants
81294	; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	; duplication/deletion variants
81297	; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	; known familial variants
81300	; duplication/deletion variants
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	; known familial variants
81319	; duplication/deletion variants
81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

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Policy History:

Medical Policy Panel, September 2018
Medical Policy Administration Committee, October 2018
Medical Policy Group, September 2018 **(9)**: Individual policy created for genetic testing for Lynch Syndrome and Peutz-Jeghers syndrome, removed related key points, descriptions, policy statements, references, and codes from medical policy #133; 2018 Updates to policy statement, policy guidelines, key points, description, references; added juvenile polyposis syndrome; expanded coverage criteria into policy statements; other history prior to October 2018 can be found on policy #133
Medical Policy Administration Committee, October 2018
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