Policy Statement

Note: Initial testing for APC, MUTYH, MMR, or EPCAM genetic variants depends on the clinical situation. Testing for cases in which there are many polyps present (See policy statement and guidelines) usually begins with APC or MUTYH variants while for those with less than 10 lifetime colonic adenomas present, testing usually begins with MMR mutations. While Lynch syndrome can also be associated with colonic adenomas, it is usually much less so than seen with APC/MUTYH mutations (less than 4% of those with Lynch Syndrome [LS] MMR mutations have 10 or more adenomas).

If initial testing is negative, further testing is not automatic, but based on the clinical situation. That is, if initial testing for APC is negative, MMR testing is not automatic; and if initial MMR testing is negative, APC testing is not always needed as a next step.

Some limited panel testing may be allowed as an alternative to individual gene testing (see Panel Testing below)

Adenomas are a type of polyp. There are different kinds of both polyps and adenomas. Adenomas are benign, but some can go on to become cancerous.

APC Testing
Genetic testing for APC gene variants may be considered medically necessary in any of the following patients:

- At-risk relatives (first or second degree) of patients with familial adenomatous polyposis (FAP) or a known APC variant. Known variant testing should be limited to that (site specific) analysis only, rather than the whole gene
- Personal history of 20 or more adenomas
- Personal history of between 10 to 20 polyps and one of the following:
  - First or second degree relative with more than 20 polyps
  - Other high-risk features as defined by a personal history of desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal or bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE)

MUTYH Testing
Genetic testing for MUTYH gene variants may be considered medically necessary in the following patients, when either of the following criteria is met:

- At-risk relatives (first or second degree) of individuals with a known MUTYH gene variant (single site analysis only)
- A negative result for APC gene variants (when the criteria for approval of APC testing was met)

The following may also be considered as high risk features for MUTYH gene variants:

- At least 5 serrated polyps (includes hyperplastic polyps, sessile serrated adenomas or polyps, and traditional serrated adenomas) proximal to the sigmoid colon with 2 or more greater than 10 millimeters (mm)
- 20 or more serrated polyps of any size distributed throughout the colon

Note: A family history of no parents or children with FAP is consistent with MUTYH-Associated Polyposis (MAP, which is autosomal recessive).
Mismatch Repair (MMR) Gene and EPCAM Testing
Genetic testing for Lynch Syndrome (LS), also known as Hereditary Nonpolyposis Colorectal Cancer (HNPC), MMR genes (MLH1, MSH2, MSH6, PMS2; both initial sequencing and for deletions and duplications) and the EPCAM gene may be considered medically necessary in patients with any of the following* (family history is first or second degree relatives):
- Family history of a known LS mutation. Variant single site analysis only
- Personal or family history of colorectal or endometrial cancer diagnosed before 50 years
- Personal history of colorectal or endometrial cancer at any age with tumor showing evidence of mismatch repair deficiency, either by microsatellite instability (MSI) or loss of mismatch repair protein expression by Immunohistochemical (IHC) analysis
- Personal or family history of at least 1 person with colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-related tumor in the same person
- Personal or family history of at least 2 people with LS-related tumors and at least 1 diagnosed before 50 years of age
- Personal or family history of at least 3 people with LS-related tumors, regardless of age
- A 5% or more risk of having an MMR gene mutation based on predictive models (e.g., PREMM5, MMRpro, MMR predict) as documented in the medical record (See policy guidelines for calculators)
- No diagnosis of colorectal cancer (CRC) but with a family history meeting the Amsterdam criteria, when no affected family members have been tested for MMR variants (See policy guidelines; Revised Bethesda criteria are included in the above criteria)

*BRAF V600E or MLH1 Promoter Methylation
Genetic testing for BRAF V600E or MLH1 promoter methylation may be considered medically necessary to exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a colorectal cancer (CRC) tumor on immunohistochemical (IHC) analysis (See Policy Guidelines section).

SMAD4 and BMPR1A Testing
Genetic testing for SMAD4 and BMPR1A gene variants may be considered medically necessary when any one of the following major criteria (solid bullets) is met:
- Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
  - At least 3 to 5 juvenile polyps in the colon
  - Multiple juvenile polyps in other parts of the gastrointestinal tract
  - Any number of juvenile polyps in a person with a known family history of juvenile polyps
- At-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome

STK11 Testing
Genetic testing for STK11 gene variants may be considered medically necessary when any one of the following major criteria (solid bullets) is met:
- Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
  - Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine

*The Revised Bethesda criteria are included in the reasons for approval

Lynch syndrome-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
Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
- Family history of Peutz-Jeghers syndrome
- At-risk relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome

Genetic testing for Lynch syndrome that does not meet the medical necessity criteria is considered investigational.

Panel Testing
Limited genetic panels (such as for MMR genes and EPCAM) may be considered medically necessary as an alternative to serial testing of individual genes when criteria are met for genetic testing of hereditary colorectal cancer. An example of such limited tests include the Colaris® panel from Myriad laboratories.

Large multi-gene panels including multiple genes that are not highly associated with hereditary colorectal cancer (see Policy Guidelines) are considered investigational.

Policy Guidelines

Testing related to hereditary breast and ovarian cancer, see Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers.

Panel testing related to non-small-cell lung cancer, see Blue Shield of California Medical Policy: Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy).

Panel testing related to cancers other than breast, ovarian, colorectal, and non-small-cell lung cancer, see Blue Shield of California Medical Policy: Genetic Panel Testing for Susceptibility to Hereditary Cancers.

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 or second 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.

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

In many cases, genetic testing for MUTYH gene variants could first target the specific variants Y165C and G382D, which account for more than 80% of variants in white populations, and subsequently, proceed to sequence only as necessary. Full sequence testing of the entire gene could be done if the initial testing is negative. However, in other ethnic populations, proceeding directly to sequencing is appropriate. Full gene testing is most commonly requested and can be approved without doing the common variants first.

Hamartomatous and Serrated Polyps
Two or more hamartomatous polyps or five or more serrated polyps may need different genetic testing (see NCCN guidelines).

Evaluation for Lynch Syndrome
For patients with colorectal cancer (CRC) being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test or the immunohistochemical (IHC) test (with or without BRAF
gene variant testing), of tumor tissue would ideally be done first, before mismatch repair (MMR) gene testing. Both MSI and IHC testing are not necessary, since they test for similar problems. High MSI or low IHC results would suggest a need for further 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 (See BRAF V600E below). MMR testing may still be needed, and can be approved without MSI or IHC test results.

MLH1 and MSH2 variants are most common, but testing is usually done in a panel that includes MSH6 and PMS2 and sometimes EPCAM. Standard sequencing methods will not detect large deletions or duplications so testing for large deletions or duplications is appropriate and is usually done at the same time as initial MMR sequence testing.

**BRAF V600E or MLH1 Promoter Methylation**

Lack of expression of MLH1 (a repair gene) can be due to aberrant (hyper) methylation of the promoter of the MLH1 proteins. This methylation (or hypermethylation) of the promoter silences expression of the MLH1 gene (and occasionally MSH2), and occurs only in tumor tissue (somatic, not germline cancers). But, abnormal IHC testing (low, or lack of the repair proteins) just shows a lack of MLH1 activity in either case. It would not be clear if that was from a genetic (germline, inherited) loss of the protein or because it is silenced by the abnormal promoter methylation in the tumor (somatic). BRAF V600E (and MLH1 promoter methylation) testing can help with whether the lack of expression of MLH1 is from a local tumor issue or inherited problem. Ideally, if IHC testing on the tumor is low, then BRAF V600E or MLH1 promoter methylation testing would be done before moving on to the MMR genetic testing. MMR testing would then be done if there is no methylation found (negative MLH1 methylation). If hypemethylation is found then the abnormal IHC result is more likely due to the somatic (local) tumor issue than due to an inherited problem with the MMR genes.

**Amsterdam II Clinical Criteria**

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

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

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

- **PREMM5**: [http://premm.dfci.harvard.edu/](http://premm.dfci.harvard.edu/)
- **MMRpro**: [http://4.utsouthwestern.edu/breasthealth/cagene/](http://4.utsouthwestern.edu/breasthealth/cagene/)
  Registration for this site is required at the University of Texas Southwestern Medical Center
- **MMRpredict**: [http://hnpccpredict.hgu.mrc.ac.uk/](http://hnpccpredict.hgu.mrc.ac.uk/)
Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Humany Genome Organization, and by the Human Genome Variation Society itself.

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

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

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

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

Coding
There are specific CPT codes for genetic testing of APC:
- 81201-81203: APC genetic testing code range

There are specific CPT codes for genetic testing of MLH1, MSH2, MSH6, PMS2, and microsatellite instability:
- 81288: MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
- 81292-81294: MLH1 genetic testing code range
- 81295-81297: MSH2 genetic testing code range
- 81298-81300: MSH6 genetic testing code range
- 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
• **81317-81319**: PMS2 genetic testing code range

There is also a specific CPT code for testing of BRAF V600 variant(s):
• **81210**: BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)

The following CPT code includes testing for EPCAM:
• **81403**: Molecular Pathology Procedure Level 4. EPCAM (epithelial cell adhesion molecule) (e.g., Lynch syndrome), duplication/deletion analysis

Genetic testing for colon cancer is not widely available and is most commonly performed by commercial reference labs or research labs dedicated to genetic testing in general.

Associated genetic counseling performed by a trained genetic counselor would be coded using the following CPT code:
• **96040**: Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

Genetic counseling performed by a physician is coded using the appropriate CPT evaluation and management codes.

**Description**

Genetic testing is available for both those with and those at risk for various types of hereditary cancer. This review evaluates genetic testing for hereditary colorectal cancer and polyposis syndromes, including familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), MUTYH-associated polyposis (MAP), Lynch syndrome–related endometrial cancer, juvenile polyposis syndrome, and Peutz-Jeghers syndrome.

**Related Policies**

• KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

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

Rationale

Background

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

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

Germline variants in the adenomatous polyposis coli (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 a 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 similar to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH variants are associated with a cumulative CRC risk of about 80% by age 70, whereas the monoallelic MUTYH variant–associated risk of CRC appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (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.\(^4\)\(^5\) However the risk varies by genotype. It occurs as a result of germline variant in the mismatch repair (MMR) genes that include MLH1, MSH2, MSH6, and PMS2. In approximately 80% of cases, the variants are located in the MLH1 and MSH2 genes, while 10% to 12% of variants are located in the MSH6 gene and 2% to 3% in the PMS2 gene. Additionally, variants in 3 additional genes (MLH3, PMS1, EX01) have been implicated with Lynch Syndrome. Notably, in individuals meeting the various clinical criteria for Lynch syndrome, 50% of individuals have a variant in the MLH1, MSH2, MSH6, and PMS2 genes. The lifetime risk of CRC is nearly 80% in individuals carrying a variant in one of these genes.

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

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

The phenotype tests used to identify individuals who may be at a high-risk of Lynch syndrome are explained next. The first screening test measures MSI. As a result of variance in the MMR gene family, the MMR protein is either absent or deficient, resulting in an inability to correct DNA replication errors causing MSI. Approximately 80% to 90% of Lynch syndrome CRC tumors have MSI. The National Cancer Institute has recommended screening for 5 markers to detect MSI (Bethesda markers). MSI detection in 2 of these markers is considered a positive result or “high probability of MSI”.\(^6\)

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

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

Both MSI and IHC have a 5% to 10% false-negative rate. MSI testing performance depends on the specific MMR variant. MSI screening has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6 and a specificity of about 90% for each. The specificity of MSI testing is low because approximately 10% of sporadic CRCs are MSI-positive due to somatic hypermethylation of the MLH1 promoter. Additionally, some tumors positive for MSH6 variants are associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR variant testing.\(^7\)\(^8\) IHC screening has sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for each.
Screening of tumor tissue from patients enables genetic testing for a definitive diagnosis of Lynch syndrome and leads to counseling, cancer surveillance (e.g., through frequent colonoscopic or endometrial screening examinations), and prophylaxis (e.g., risk-reducing colorectal or gynecologic surgeries) for CRC patients, as well as for their family members.

Genetic testing for an MMR gene variant is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2. The BRAF gene is often mutated in CRC when a particular BRAF variant (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present; to date, no MLH1 gene variants have been reported. 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, results in transcriptional “read-through” and subsequent hypomethylation of the nearby and downstream MSH2 promoter. This hypomethylation 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), Revised 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 CRC patients for Lynch syndrome, using a screening strategy based on MSI or IHC (with or without BRAF) followed by sequencing in screen-positive patients. This recommendation includes genetic testing for the following types of patients:

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

### Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant genetic disorder characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract. It is rare, with an estimated incidence of 1 in 100,000 to 160,000. Generalized juvenile polyposis refers to polyps in the upper and lower gastrointestinal tract, and juvenile polyposis coli refers to polyps of the colon and rectum. Those with JPS are at a higher risk for colorectal and gastric cancer. Approximately 60% of patients with JPS have a germline variant in 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.

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

### Diagnosis

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

### Peutz-Jeghers Syndrome

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

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

**Diagnosis**

A clinical diagnosis of PJS is made if an individual meets two or more of the following criteria: presence two or more histologically confirmed PJ polyps of the small intestine or characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, fingers, or family history of PJS. Individuals who meet clinical criteria for PJS should undergo genetic testing for a germline variant in the STK11 gene for a confirmatory diagnosis of PJS and counseling at-risk family members. 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.

**Literature Review**

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

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

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

**Clinical Context and Test Purpose**

The purpose of genetic testing for familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP) is to:

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

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

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

**Patients**

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

**Interventions**

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

**Comparators**

The following practice is currently being used to make decisions about managing FAP and MAP: no genetic testing.

**Outcomes**

The potential beneficial outcomes of primary interest would be the early detection of colorectal cancer (CRC) and appropriate and timely interventional strategies (e.g., endoscopic resection, colectomy) to prolong life.
The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

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

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

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

- Reported on the analytic sensitivity and specificity and/or diagnostic yield of the test.

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

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

The evidence review for FAP genetic testing was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (1998). The additional information on attenuated FAP and on MAP diagnostic criteria and genetic testing is based on information from GeneReviews and from several publications that build on prior, cited research.

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

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

**Section Summary: Clinically Valid**
The analytic and clinical sensitivity and specificity for APC and MUTYH are high. About 90% of pathogenic variants in classical FAP are detected by sequencing while 8% to 12% of pathogenic variants are detected by deletion and duplication testing. Among Northern European whites, 85% of pathogenic MUTYH variants are detected by the 2 variant test, and 98% of pathogenic MUTYH variants are detected by full gene sequencing. The likelihood of detecting an APC pathogenic variant is highly dependent on the severity of colonic polyposis and family history.
Detection rates are higher in classic polyposis (88%) than in nonclassical FAPs such as attenuated colonic phenotypes (57%) or MAP (33%).

**Clinical Useful**
A test is clinically useful if use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified assessing the clinical utility of genetic testing for FAP and MAP.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of patients requiring a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome may have clinical utility:
- If the test supports the clinical diagnosis of an attenuated disease, the protocol for endoscopic surveillance is affected and, depending on the situation, may avoid more frequent but unnecessary surveillance or necessitates more frequent surveillance.

Genetic testing of at-risk relatives of patients with FAP and/or a known APC variant may have clinical utility:
- If, in the absence of genetic testing, the diagnosis of colorectal polyposis in at-risk relatives of patients with FAP and/or a known APC variant can only be established by colonoscopy and subsequent histologic examination of removed polyps, which are burdensome.
- If results are negative, the test results may provide release from the intensified screening program resulting in psychological relief.

A TEC Assessment (1998)37 offered the following conclusions:
- Genetic testing for FAP may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.
- At-risk subjects are considered to be those with greater than 10 adenomatous polyps or close relatives of patients with clinically diagnosed FAP or of patients with an identified APC variant.
- The optimal testing strategy is to define the specific genetic variant in an affected family member and then test the unaffected family members to see if they have inherited the same variant.

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjork et al (2000)34</td>
<td>Observational: 195 confirmed cases of FAP underwent ileorectal anastomosis and followed for, on average, 14 y</td>
<td>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...</td>
</tr>
</tbody>
</table>
Study | Study Design and Population | Results |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Järvinen (1992)</td>
<td>Observational: 251 individuals from 81 affected families; 76 individuals diagnosed during family screening vs 116 symptomatic individuals with probands</td>
<td>substantial risk of developing cancer even after surgery</td>
</tr>
<tr>
<td>Vasen et al (1990)</td>
<td>Observational: CRC rate compared in 230 confirmed FAP cases; 104 symptomatic and 126 at-risk family members identified by screening</td>
<td>65.5% of symptomatic cases had CRC vs 6.6% cases among those screened during family screening</td>
</tr>
</tbody>
</table>

**Section Summary: Clinically Useful**

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

**Lynch Syndrome and CRC Genetic Testing**

**Clinical Context and Test Purpose**

The purpose of genetic testing for Lynch syndrome is to:

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

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

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

**Patients**

The relevant populations of interest are patients diagnosed with colorectal or endometrial cancer or at-risk relatives of patients with a diagnosed Lynch syndrome and/or a known MMR variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria or those requiring a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome.

**Interventions**

The relevant intervention is genetic testing for the MLH1, MSH2, MSH6, PMS2, EPCAM, and/or BRAF V600E genes. Commercial testing is available from numerous companies.

**Comparators**

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

**Outcomes**

The potential beneficial outcomes of primary interest would be early detection of Lynch syndrome and appropriate and timely interventional strategies (e.g., increased surveillance, endoscopic resection, colectomy) to prolong life.
The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse effects from that treatment or undertreatment.

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

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

**Study Selection Criteria**
For the evaluation of clinical validity of the genetic test, studies that met the following eligibility criterion were considered:
- Reported on the analytic sensitivity and specificity and/or diagnostic yield of the test.

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

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

Microsatellite instability (MSI) and immunohistochemical (IHC) screening tests for MMR variants have similar sensitivity and specificity. MSI screening has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6 and a specificity of about 90% for each. IHC screening has a sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for each.

The evidence for Lynch syndrome genetic testing in patients with CRC is based on an evidence report conducted for the Agency for Healthcare Research and Quality by Bonis et al (2007), a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009), and an EGAPP recommendation (2009) for genetic testing in CRC. Based on the Agency for Healthcare Research and Quality report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for MMR variants in patients already diagnosed with CRC:
- Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for MMR variant testing and should not be used as a sole determinant or screening test.
- Optional BRAF testing can be used to reduce the number of patients, who are negative for MLH1 expression by IHC, needing MLH1 gene sequencing, thus improving efficiency without reducing sensitivity for MMR variants.

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

Table 2. Diagnostic Results of the Different Screening Approaches

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

CI: confidence interval.

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

Several studies have characterized EPCAM deletions, established their correlation with the presence of EPCAM-MSH2 fusion messenger RNAs (apparently nonfunctional) and with the presence of MSH2 promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM variants with Lynch-like disease in families.11-16 Because studies differed 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 MS-high tumor tissue. Kempers et al (2011) reported that carriers of an EPCAM deletion had a 75% (95% CI, 65% to 85%) cumulative risk of CRC by age 70 years, which did not differ significantly from that of carriers of an MSH2 deletion (77%; 95% CI, 64% to 90%); mean age at diagnosis was 43 years.60 However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0% to 27%) by age 70 compared with carriers of an MSH2 variant (51%; 95% CI, 33% to 69%; p<0.001).

Bouzourene et al (2010) analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC and 16 patients with Lynch syndrome.10 A BRAF variant was not found in any of the Lynch syndrome patients. MLH1 promoter methylation was only present in 1 Lynch syndrome patient. However, 8 of the 11 sporadic CRC patients had the BRAF variant, and all 11 patients were MLH1 methylated, suggesting patients with BRAF variants could be excluded from germline testing for Lynch syndrome. Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients.61 MLH1 and PMS2 protein stains were absent in 65 patients who were subsequently tested for BRAF variant. Thirty-six (55%) of the 65 patients had the BRAF V600E variant, thus eliminating the need for further genetic testing or counseling for Lynch syndrome. Capper et al (2013) reported on a technique of V600E IHC testing for BRAF variants on a series of 91 stratified as high MSI CRC patients.62 The authors detected BRAF-mutated CRC with 100% sensitivity and 98.8% specificity. V600E positive lesions were detected in 21% of MLH1-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore, V600E IHC testing for BRAF could be an alternative to MLH1 promoter methylation analysis. To summarize, BRAF V600E variant or MLH1 promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH1 protein expression. The presence of BRAF V600E or absence of MLH1 protein expression due to MLH1 promoter methylation rarely occurs in Lynch syndrome and would eliminate the need for further germline variant analysis for a Lynch syndrome diagnosis.

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 70.64 Risks do not appear to appreciably increase until after age 40. In a prospective study by Leenen et al (2012), 179 consecutive endometrial cancer patients 70 years of age or younger were analyzed for MSI, using IHC for expression of 4 MMR proteins, MMR gene methylation status, and BRAF variants.65 Results are presented in Table 3; 92% of patients were older than 50 years of age.
Table 3. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N</th>
<th>Percent (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsatellite stable and normal protein staining</td>
<td>137</td>
<td>76</td>
</tr>
<tr>
<td>MSI-H and MLH1 absent</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Sporadic MSI-H</td>
<td>31</td>
<td>17 (13 to 24)</td>
</tr>
<tr>
<td>Likely to have Lynch syndrome</td>
<td>11</td>
<td>6 (3 to 11)</td>
</tr>
<tr>
<td>Variant-positive</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No variant found</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Refused further DNA testing</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

MSI-H: high microsatellite instability.

** Clinically Useful **

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

** Direct Evidence **

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing the clinical utility of genetic testing for Lynch syndrome.

** Chain of Evidence **

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of patients with colon or endometrial cancer to detect Lynch syndrome has clinical utility:

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

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

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

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

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

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

1. The chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first-
and second-degree relatives of patients with Lynch syndrome who have a known MMR variant.

2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients.66-72 About half of the relatives received counseling, and 95% of them chose MMR gene variant testing. Among those positive for MMR gene variants, uptake of colonoscopic surveillance beginning at age 20 to 25 years was high at 53% to 100%.

   - One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance vs those who did not.
   - Surveillance and prevention for other Lynch syndrome cancers.

3. The chain of evidence from descriptive studies and expert opinion is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., the index patient).

   1. Subtotal colectomy is recommended as an alternative to segmental resection but has not been shown superior in follow-up studies.
   2. Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.

   - Surveillance and prevention for other Lynch syndrome cancers:
     1. While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In a retrospective study by Schmeler et al (2006), 315 women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% develop ovarian cancer.73
     2. In a study by Bouzourene et al (2010), surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown.10 Transvaginal ultrasound is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, transvaginal ultrasound in conjunction with endometrial biopsy has been recommended for surveillance.
     3. Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supporting evidence.

In early documentation of the natural history of CRC in highly selected families with a strong history of hereditary CRC, Fitzgibbons et al (1987) indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, in those with CRC.74 As a result, the Cancer Genetic Studies Consortium (1997) recommended that if CRC is diagnosed in patients with an identified variant or a strong family history, a subtotal colectomy with ileorectal anastomosis should be considered as an option to segmental resection.75 Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. Van Dalen et al (2003) suggested that subtotal colectomy with ileorectal anastomosis markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance.76 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.77 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.78 The societies’ review also recommended offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch anal anastomosis or anterior proctosigmoidectomy with primary reconstruction. The
rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross-sectional cohort: Examined adoption of risk-reduction strategies using a one-time questionnaire in 77 women at risk of LS-associated endometrial cancer.</td>
<td>Proportion of women engaging in endometrial cancer risk-reduction strategy before genetic testing: 26/40 (65%). At 1-y follow-up, 16/16 (100%) MMR variant carriers were adherent to guidelines for risk-reduction, 9 (56%) of whom had had a prophylactic hysterectomy. By 3 y, 11/16 (69%) MMR variant carriers had a prophylactic hysterectomy. Among women with negative or uninformative genetic test results, none had a prophylactic hysterectomy after testing.</td>
</tr>
<tr>
<td>Engel et al (2010)</td>
<td>Prospective cohort: Assessed efficacy of annual colonoscopic surveillance in 1126 at-risk individuals from families with LS.</td>
<td>99 CRCs found in 90 individuals; 71 were diagnosed by surveillance colonoscopies. Median time between CRCs detected through follow-up colonoscopy and preceding colonoscopy was 11.3 mo.</td>
</tr>
<tr>
<td>Järvinen et al (2009)</td>
<td>Observational; 609 individuals from 57 LS families; 242 variant-positive and 367 variant-negative followed for cancer incidence over a mean of 11.5 y.</td>
<td>No increase in cancer mortality in variant-positive vs-negative individuals; 74 variant-positive individuals had adenomas removed; 48 variant-positive women had prophylactic hysterectomy.</td>
</tr>
<tr>
<td>Dove-Edwin et al (2005)</td>
<td>Prospective observational; 554 individuals from 290 at-risk families with HNPCC or MMR variants followed for 16 y.</td>
<td>Estimated 72% decrease in CRC death in screened individuals.</td>
</tr>
<tr>
<td>De Vos tot Nederveen Cappel et al (2002)</td>
<td>Observational; 857 at-risk individuals from 114 HNPCC- or MMR-positive families.</td>
<td>10-y cumulative risk of CRC, 15.7% vs 3.4% for partial vs subtotal colectomy.</td>
</tr>
<tr>
<td>Syngal et al (1998)</td>
<td>Decision analysis model: Assessed impact of decision about immediate prophylactic colectomy, delayed colectomy, or endoscopic surveillance at the time of a positive result on genetic testing.</td>
<td>Compared with no intervention, all risk-reduction strategies led gains in life expectancy from 13.5 y for surveillance to 15.6 y for prophylactic proctocolectomy at 25 y of age. Also, surveillance led to QALY gain of 3.1 y vs 0.3 y with subtotal colectomy.</td>
</tr>
<tr>
<td>Järvinen et al (1995)</td>
<td>Observational; 252 at-risk individuals from 20 of 22 families with MMR variants invited for colonoscopy screening every 3 y; 133 agreed; 118 declined. Of those who declined, 8 (15%) had screening examinations outside of the study.</td>
<td>Screening vs nonscreening: Incidence of CRC: 4.5% (n=6) vs 11.9% (n=14) (p=0.03); 6 vs 12 deaths within 10 y (p=0.08).</td>
</tr>
</tbody>
</table>

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

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

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

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

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

Females with Lynch syndrome who choose risk-reducing surgery are encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. In a retrospective cohort study, Obermaier et al (2010) found that hysterectomy improved survival among female colon cancer survivors with Lynch syndrome.88 This study also estimated that, for every 100 women diagnosed with Lynch syndrome–associated CRC, about 23 would be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Data on variant-specific risks have suggested that prophylactic gynecologic surgery benefits for carriers of MSH6 variants may offer less obvious benefits compared with harms, because the lifetime risk of endometrial cancer is lower than for carriers of MLH1 or MSH2 variants, and the lifetime risk of ovarian cancer is similar to the risk for the general population.64

However, for carriers of the EPCAM deletion, 3 studies (2011, 2012) reported on 3 cases of endometrial cancer in 103 female carriers who did not undergo a preventative hysterectomy.60,89,90 Women with EPCAM deletions consequently have a 1-fold lower lifetime risk of developing endometrial cancer than with carriers with an MMR variant. This might support a clinical management scenario rather than prophylactic surgery.99 An alternative to prophylactic surgery is surveillance for endometrial cancer using transvaginal ultrasound and endometrial biopsy. Evidence has suggested that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet has indicated surveillance reduces mortality due to endometrial cancer.91 Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.91

Section Summary: Clinically Useful

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

Genetic Testing for Juvenile polyposis syndrome and Peutz-Jeghers syndrome: Clinical Context and Test Purpose

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

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

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

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

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

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

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

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

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

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

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

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

- Reported on the diagnostic yield of the test.

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

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
Table 6 summarizes the clinical utility studies assessing genetic testing for JPS and PJS.

**Table 6. Summary of Clinical Validity Studies Assessing Genetic Testing for JPS and PJS**

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

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

**Section Summary: Clinically Valid**

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

**Clinical Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing the clinical utility of genetic testing for JPS and PJS.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of patients with suspected JPS and PJS has clinical utility:
- To make decisions about a preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis, segmental colectomy).

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

Table 7 summarizes clinical utility studies assessing genetic testing for JPS and PJS.
### Table 7. Summary of Clinical Utility Studies for Genetic Testing for JPS and PJS

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aytac et al (2015)(^97)</td>
<td>Observational: 35 patients had germline variants in BMPR1A (8 patients) or SMAD4 (27) with a median follow-up of 11 y</td>
<td>No patient was diagnosed with cancer in the BMPR1A group, whereas 4 men with a SMAD4 variant developed GI (n=3) or extraintestinal (n=1) cancer. The GI cancer risk in patients with JPS and a SMAD4 variant was 11% (3/27).</td>
</tr>
<tr>
<td>Resta et al (2013)(^98)</td>
<td>Observational: 119 patients with PJS</td>
<td>Cancer occurred in 31/119 patients (RR for overall cancer risk, 15.1); mean age at first cancer diagnosis was 41 y. Kaplan-Meier estimates for overall cumulative cancer risks were 20%, 43%, 71% and 89% at age 40, 50, 60, and 65 y, respectively.</td>
</tr>
<tr>
<td>Lier et al (2010)(^36)</td>
<td>Systematic review: 21 original articles, 20 cohort studies, and 1 meta-analysis (total N=1644 PJS patients)</td>
<td>349 patients developed 384 malignancies at average age of 42 y. Lifetime risk for any cancer varied between 37% and 93% with RRs ranging from 9.9 to 18 vs the general population.</td>
</tr>
<tr>
<td>Salloch et al (2009)(^99)</td>
<td>Observational: 31 patients with PJS; STK11 variants in 16/22 families</td>
<td>10 carcinomas detected in 6 patients resulting in a cancer risk of 65% up to the age of 65 y; surveillance strategy detected 50% of cancers (n=6) at an early potentially curable stage</td>
</tr>
<tr>
<td>Brosens et al (2007)(^29)</td>
<td>Observational: 84 patients with JPS contributing 1652.2 person-years of follow-up vs general population of the U.S. (SEER data)</td>
<td>RR of CRC was 34.0 (95% CI, 14.4 to 65.7); cumulative life-time risk for CRC was 38.7%; mean age of diagnosis of CRC, 43.9 y</td>
</tr>
</tbody>
</table>

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

### Section Summary: Clinically Useful

Direct evidence of the clinical utility for genetic testing of JPS or PJS is not available. Genetic testing of patients with suspected JPS or PJS or individuals who are at-risk relatives of patients suspected of or diagnosed with a polyposis syndrome or PJS may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy.

### Summary of Evidence

For individuals who are suspected of attenuated FAP, MAP, and Lynch syndrome who receive genetic testing for APC, or are at-risk relatives of patients with FAP who receive genetic testing for MUTYH after a negative APC test result, the evidence includes a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. For patients with an APC variant, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. A related familial polyposis syndrome, MAP syndrome, is associated with variants in the MUTYH gene. Testing for this genetic variant is necessary when the differential diagnosis includes both FAP and MAP because distinguishing between the 2 leads to different management strategies. Depending on presentation, Lynch syndrome may be part of the same differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

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

For individuals who are suspected of JPS or PJS or (2) are at-risk relatives of patients suspected of or diagnosed with JPS or PJS who receive genetic testing for SMAD4, BMPR1A, or STK11 genes, respectively, the evidence includes multiple observational studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between SMAD4 and BMPR1A and STK11 variants with JPS and PJS, respectively. Direct evidence of clinical utility for genetic testing of a JPS or PJS is not available. Genetic testing may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies and 3 academic medical centers in 2009. In general, those providing input agreed with the overall approach described in this policy.
Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines (v.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, and PMS2. NCCN guidelines also indicate BRAF V600E testing or MLH1 promoter methylation testing may be used when MLH1 is not expressed in the tumor on immunohistochemical analysis to exclude a diagnosis of Lynch syndrome. These guidelines also address familial adenomatous polyposis (classical and attenuated) and MUTYH-associated polyposis and are consistent with the information provided in this evidence review.

NCCN guidelines for colon cancer (v.3.2018) 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 secondary 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 on 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 8 and 9.

Table 8. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome (Category 2A Recommendations)

<table>
<thead>
<tr>
<th>Site</th>
<th>Lifetime Risk, %</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>45-50</td>
<td>Mammogram and breast MRI annually</td>
<td>≈25 y</td>
</tr>
<tr>
<td>Colon</td>
<td>39</td>
<td>Colonoscopy every 2-3 y</td>
<td>Late teens</td>
</tr>
<tr>
<td>Stomach</td>
<td>29</td>
<td>Upper endoscopy every 2-3 y</td>
<td>Late teens</td>
</tr>
<tr>
<td>Small intestine</td>
<td>13</td>
<td>Small bowel visualization (CT or MRI enterography or video capsule endoscopy baseline at 8-10 y with follow-up interval based on findings but at least by age 18, then every 2-3 y, though this may be individualized, or with symptoms)</td>
<td>≈8 to 10 y</td>
</tr>
</tbody>
</table>
Table 9. Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome (Category 2A Recommendations)

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

CT: computed tomography; MRI: magnetic resonance imaging.

<sup>a</sup> 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 (2015) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.<sup>26</sup>

For Lynch syndrome, the College recommended:

“All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency.

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

Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF variant or hypermethylation of MLH1), a known family variant associated with LS [Lynch syndrome], or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.<sup>103</sup>

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

For adenomatous polyposis syndromes, the College recommended:

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

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

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

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

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

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

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

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

American Society of Clinical Oncology and Society of Surgical Oncology
The American Society of Clinical Oncology (2015) concluded the European Society for Medical Oncology clinical guidelines published in 2013 were based on the most relevant scientific evidence and therefore endorsed them with minor qualifying statements (in bold italics).104 The recommendations as related to genetic testing hereditary CRC syndromes are summarized below:

- “Tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines.
- If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.
- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1).
- Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis...
- Patients with multiple colorectal adenomas should be considered for full germline genetic testing of APC and/or MUTYH.
Germline testing of MUTYH can be initiated by screening for the most common mutations (G396D, Y179C) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered.

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

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 10.

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

NCT: national clinical trial.

References


Documentation for Clinical Review

Please provide the following documentation (if when requested):

- History and physical and/or consultation notes including:
  - Laboratory invoice/order indicating specific test(s)/panel(s) and associated procedure codes
  - Personal and/or family history of cancer (if applicable) including: family relationship, cancer site(s), age at diagnosis
  - Preliminary diagnosis and prognosis
  - Specific test(s) requested and clinical reason/justification for testing
  - Treatment plan
  - Genetic counseling/professional results (if available)
  - Laboratory and/or Pathology report(s) (e.g., APC gene mutations, MSH2, MMR mutations)

Post Service

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
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<td></td>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
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<td>81203</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
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<td>81210</td>
<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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<tr>
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<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
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<td>81293</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81299</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<tr>
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<td>81300</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81301</td>
<td>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</td>
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<tr>
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<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81401</td>
<td>Molecular Pathology Procedure Level 2</td>
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<td>81403</td>
<td>Molecular Pathology Procedure Level 4</td>
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<td></td>
<td>81406</td>
<td>Molecular Pathology Procedure Level 7</td>
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<tr>
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<td>81432</td>
<td>Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53</td>
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<tr>
<td></td>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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</table>

**HCPCS**: None

**ICD-10 Procedure**: None
Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>10/14/1998</td>
<td>New Policy Adoption</td>
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<tr>
<td>05/01/2001</td>
<td>Policy Review</td>
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<tr>
<td>02/02/2010</td>
<td>Policy revision with position change</td>
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<tr>
<td>06/28/2010</td>
<td>Policy revision with position change Coding update</td>
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<td>07/02/2010</td>
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<td>04/12/2012</td>
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<td>02/22/2013</td>
<td>Coding Update</td>
<td>Administrative Review</td>
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<td>03/28/2014</td>
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<tr>
<td>10/31/2014</td>
<td>Policy title change from Genetic Testing for Colorectal Cancer</td>
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<td>01/30/2015</td>
<td>Coding Update</td>
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<td>09/01/2018</td>
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<td>11/01/2018</td>
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<tr>
<td>01/01/2019</td>
<td>Policy statement clarification</td>
<td>Administrative Review</td>
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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.
Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.