Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Policy #  00190
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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

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

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

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

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

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

- Patients with a differential diagnosis of attenuated FAP (AFAP) vs. MUTYH-associated polyposis (MAP) vs. Lynch syndrome and a negative result for polyposis coli (APC) gene mutations. Family history of no parents or children with familial adenomatous polyposis (FAP) is consistent with MUTYH-associated polyposis (MAP) (autosomal recessive).

Based on the review of available data, the Company may consider genetic testing for mismatch repair (MMR) gene mutations in the following patients to be eligible for coverage:

- Patients with colorectal cancer/carcinoma (CRC) who meet the revised Bethesda Guidelines, for the diagnosis of Lynch syndrome
- Patients with endometrial cancer and 1 first-degree relative diagnosed with a Lynch-associated cancer, for the diagnosis of Lynch syndrome.
- At-risk relatives of patients with Lynch syndrome with a known mismatch repair (MMR) mutation.
- Patients with a differential diagnosis of attenuated familial adenomatous polyposis (FAP) vs. MUTYH-associated polyposis (MAP) vs. Lynch syndrome. Whether testing begins with polyposis coli (APC) mutations or screening for mismatch repair (MMR) mutations depends upon clinical presentation.
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- Patients without colorectal cancer (CRC) but with a family history meeting the Amsterdam II or Revised Bethesda criteria, when no affected family members have been tested for mismatch repair (MMR) mutations.
- Patients with ≥5% risk of Lynch Syndrome on one of the following mutation prediction models: MMRpro, PREMM, or MMRpredict.

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

- Patients with colorectal cancer (CRC), for the diagnosis of Lynch syndrome when:
  - Tumor tissue shows lack of MSH2 expression by immunohistochemistry and patient is negative for a germline mutation in MSH2; OR
  - Tumor tissue shows a high level of microsatellite instability (MSI) and patient is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6; OR

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

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

(Note: see Background/Overview for Lynch Syndrome risk definitions, i.e. Amsterdam II Clinical Criteria and or Revised Bethesda Guidelines)

Based on the review of available data, the Company may consider genetic testing for BRAF V600E or MLH1 promoter methylation to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer (CRC) on immunohistochemical (IHC) analysis to be eligible for coverage.

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

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

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

Based on the review of available data, the Company may consider genetic testing for all other gene mutations for Lynch syndrome or colorectal cancer (CRC) to be investigational.*
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Background/Overview
Genetic testing is available for both affected individuals, as well as those at risk, for various types of hereditary cancer. This policy describes genetic testing for FAP, Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC), MAP, and Lynch syndrome-related endometrial cancer.

There are currently two well-defined types of hereditary CRC, FAP and Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer or HNPCC). Lynch syndrome has been implicated in some endometrial cancers as well.

Familial Adenomatous Polyposis and Associated Variants
Familial adenomatous polyposis typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will go on to develop CRC. The mean age of colon cancer diagnosis in untreated individuals is 39 years. Familial adenomatous polyposis 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 (CHRPE). Familial adenomatous polyposis associated with these collective extraintestinal manifestations is sometimes referred to as Gardner syndrome. Familial adenomatous polyposis may also be associated with central nervous system (CNS) tumors, referred to as Turcot syndrome.

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

A subset of FAP patients may have AFAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, CRC occurring at an average age of 50-55 years, but a high lifetime risk of colorectal cancer of about 70% by age 80 years. The risk of extra-intestinal cancer is lower compared to classical FAP but still high at an estimated cumulative lifetime risk of 38% compared to the general population. Only 30% or fewer of AFAP patients have APC mutations; some of these patients instead have mutations in the MUTYH (formerly MYH) gene and are then diagnosed with MAP. MUTYH-associated polyposis occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH mutations are associated with a cumulative CRC risk of about 80% by age 70, whereas monoallelic MUTYH mutation-associated risk of CRC appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (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 mutations, and screening for mutations associated with Lynch syndrome.
It is important to distinguish among classical FAP, AFAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome.

Genetic testing for APC mutations may be considered for the following types of patients:

- Family members of patients with FAP and a known APC mutation. Those without the specific mutation have not inherited the susceptibility gene and can forego intense surveillance (although they retain the same risk as the general population and should continue an appropriate level of surveillance).
- Patients with a differential diagnosis of FAP vs. MAP vs. Lynch syndrome. These patients do not meet the clinical diagnostic criteria for classical FAP and have few adenomatous colonic polyps.
- Patients with colon cancer with a clinical picture or family history consistent with classical FAP.

**Lynch Syndrome**

Patients with Lynch syndrome have a predisposition to CRC and other malignancies as a result of an inherited mutation in a deoxyribonucleic acid (DNA) MMR gene. Lynch syndrome includes those with an existing cancer and those who have not yet developed cancer. The term “HNPCC” originated prior to the discovery of explanatory MMR mutations for many of these patients and now includes some who are negative for MMR mutations and likely have mutations in as-yet unidentified genes. For purposes of clarity and analysis, the use of Lynch syndrome in place of HNPCC has been recommended in several recent editorials and publications.

Lynch syndrome is estimated to account for 3% to 5% of all CRC and is also associated with an increased risk of other cancers such as endometrial, ovarian, urinary tract, and biliary tract cancer. Lynch syndrome is associated with a risk of developing CRC by age 70 years of approximately 27% to 45% for men, and 22% to 38% for women, after correction for ascertainment bias. Lynch syndrome patients who have CRC also have an estimated 16% risk of a second primary within 10 years.

Lynch syndrome is associated with any of a large number of possible mutations in 1 of several MMR genes, known as MLH1, MSH2, MSH6, PMS2 and rarely MLH3. Risk of all Lynch syndrome-related cancers is markedly lower for carriers of a mutation in the MSH6 and PMS2 genes, although for most cancers still significantly higher than that of the general population. Estimated cumulative risks of any associated cancer for a carrier of a mutation in any MMR gene do not begin to increase until after age 30 years.

Lynch syndrome mutations are heterozygous; that is, only one of the 2 gene alleles contains a mutation. In rare cases both alleles contain the mutation, i.e., biallelic MMR gene mutations. This unusual syndrome has been described in multiple families and is to a large extent the result of consanguinity. Children with biallelic MMR mutations may develop extra-colonic cancers in childhood, such as brain tumors, leukemias, or lymphomas. Those unaffected or surviving early malignancies are at high risk of later CRC (average age of CRC diagnosis 16.4 years). Family history may not suggest Lynch syndrome. Prior to cancer diagnosis, patients may have multiple adenomatous polyps and thus may have an initial differential diagnosis of AFAP versus MAP versus Lynch syndrome.
About 70% of Lynch syndrome patients have mutations in either MLH1 or MSH2. Testing for MMR gene mutations is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2 testing. Large gene sizes and the difficulty of detecting mutations in these genes make direct sequencing a time- and cost-consuming process. Thus, additional indirect screening methods are needed to determine which should proceed to direct sequencing for MMR gene mutations. Available screening methods are MSI testing or IHC testing. 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 slightly improve efficiency.

Mutations in MMR genes result in a failure of the MMR system to repair errors that occur during the replication of DNA in tumor tissue. Such errors are characterized by the accumulation of alterations in the length of simple, repetitive microsatellite (2 to 5 base repeats) sequences that are distributed throughout the genome, termed MSI and resulting in an MSI-high tumor phenotype. MSI testing was standardized subsequent to a 2004 National Cancer Institute (NCI) workshop. Methodologic studies have also shown the importance of laser microdissection of the tumor tissue, comparison of tumor and normal cells, and a minimum proportion of tumor in relation to the quality of the test results. While the sensitivity of MSI testing is high, the specificity is low because approximately 10% of sporadic CRC are MSI-positive due to somatic hypermethylation of the MLH1 promoter. Additionally, some tumors positive for MSH6 mutations are associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR mutation testing.

Absent or reduced protein expression may be a consequence of an MMR gene mutation. Immunohistochemical assays for the expression of MLH1, MSH2, MSH6, and PMS2 can be used to detect loss of expression of these genes and to focus sequencing efforts on a single gene. It is also possible for IHC assays to show loss of expression, and thus indicate the presence of a mutation, when sequencing is negative for a mutation. In such cases, mutations may be in unknown regulatory elements and cannot be detected by sequencing of the protein coding regions. Thus IHC may add additional information.

The BRAF gene is often mutated in CRC; when a particular BRAF mutation (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present; to date no MLH1 gene mutations have been reported. Therefore, patients negative for MLH1 protein expression by IHC, and therefore potentially positive for an MLH1 mutation, could first be screened for a BRAF mutation. 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.

Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR mutations, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria (low sensitivity but high specificity) and the Bethesda guidelines (better sensitivity but poorer specificity). 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 (EGAPP) Working Group recommended testing all newly diagnosed patients with CRC for Lynch syndrome, using a screening
strategy based on MSI or IHC (±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 mutation; family members would be tested only for the family mutation; those testing positive would benefit from early and increased surveillance to prevent future CRC.
- Patients with a differential diagnosis of Lynch syndrome vs. AFAP vs. MAP.
- 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 mutation.

Recently, novel deletions have been reported to affect the expression of the MSH2 MMR gene in the absence of a MSH2 gene mutation, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule, are responsible. The epithelial cell adhesion molecule 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 mutation is found by sequencing.

Separately from patients with EPCAM deletions, rare Lynch syndrome patients have been reported without detectable germline MMR mutations although IHC testing demonstrates a loss of expression of one of the MMR proteins. In at least some of these cases, research has identified germline "epimutations," i.e., methylation of promoter regions that control the expression of the MMR genes. Such methylation may be isolated or in conjunction with a linked genetic alteration near the affected MMR gene. The germline epimutations may arise de novo or may be heritable in either 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 non-expression, but the same is not true of germline cells. Clinical testing for Lynch syndrome-related germline epimutations is not routine but may be helpful 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 mutations MLH1, MSH2, MSH6, and PMS2 have an estimated 40-62% lifetime risk of developing endometrial cancer, as well as a 4-12% lifetime risk of ovarian cancer.

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

It is recommended that, when possible, initial genetic testing for FAP or Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the mutation found in the affected family member.
In many cases, genetic testing for MUTYH gene mutations should first target the specific mutations Y165C and G382D, which account for more than 80% of mutations in Caucasian populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

For patients with CRC being evaluated for Lynch syndrome, either the MSI test, or the IHC test with or without BRAF gene mutation testing, should be used as an initial evaluation of tumor tissue prior to MMR gene analysis. Both tests are not necessary. Consideration of proceeding to MMR gene sequencing would depend on results of MSI or IHC testing. Immunohistochemical testing in particular may help direct which MMR gene likely contains a mutation, if any, and may also provide some additional information if MMR genetic testing is inconclusive.

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

Several Clinical Laboratory Improvement Amendments (CLIA)-licensed clinical laboratories offer MMR gene mutation testing for Lynch syndrome. For example, the GeneTests website (available online at: http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2622?db=genetests) lists 187 U.S.-located laboratories that offer this service. In at least one laboratory, Lynch syndrome mutation testing is packaged under one copyrighted name. The COLARIS® test from Myriad Genetic Laboratories includes sequence analysis of MLH1, MSH2, MSH6 and PMS2; large rearrangement analysis for MLH1 MSH2, PMS2, and MSH6 large deletions/duplications; and analysis for large deletions in the EPCAM gene near MSH2. Note that there may be 2 versions of this test, the COLARIS (excludes PMS2 testing) and COLARIS Update (includes PMS2 testing). Testing is likely done in stages, beginning with the most common types of mutations. Individualized testing (e.g., targeted testing for a family mutation) can also be requested.

Similarly, GeneTests lists 15 U.S.-based CLIA-licensed clinical laboratories that provide APC mutation testing and 14 that provide MUTYH mutation testing. The COLARIS AP test from Myriad Genetic Laboratories includes DNA sequencing analysis of the APC and MUTYH genes, as well as analysis of large rearrangements in the APC gene that are not detected by DNA sequencing.

Amsterdam II Clinical Criteria (all criteria must be fulfilled).
- 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;
- FAP should be excluded in cases of colorectal carcinoma;
- Tumors should be verified by pathologic examination.
- Modifications:
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Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines). The Bethesda guidelines are felt to be more useful in identifying which patients with CRC should have their tumors tested for MSI and/or immunohistochemistry:

- CRC diagnosed in a patient who is less than 50 years-old;
- Presence of synchronous (at the same time) or metachronous (at another time i.e.- a recurrence of) CRC or other Lynch syndrome-associated tumors, regardless of age;
- CRC with high MSI histology diagnosed in a patient less than 60-years old;
- CRC diagnosed in a patient with one or more first-degree relatives with a Lynch Syndrome-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed at younger than age 50 years.
- CRC diagnosed in a patient with two or more first or second-degree relatives with Lynch Syndrome-related cancers regardless of age.

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

FDA or Other Governmental Regulatory Approval

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

Rationale/Source

Familial Adenomatous Polyposis Genetic Testing
The policy for FAP genetic testing was based on a 1998 TEC Assessment, which 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.
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- 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 mutation.
- The optimal testing strategy is to define the specific genetic mutation in an affected family member and then test the unaffected family members to see if they have inherited the same mutation.

The additional policy information on AFAP and on MAP diagnostic criteria and genetic testing is based on information from GeneReviews and from several publications that build on prior, cited research. In addition, GeneReviews summarizes clinical FAP genotype-phenotype correlations that could be used to determine different patient management strategies. The authors of the review conclude, however, that there is not yet agreement about using such correlations to direct management choices.

Testing for the APC gene mutation, i.e., testing for FAP, is considered not medically necessary in those with classical FAP. This is not medically necessary because the genetic testing is not needed to make the diagnosis of FAP in these patients. Testing for the APC mutation has no role (no purpose) in the evaluation, diagnosis, or treatment of these patients where the diagnosis and treatment are based on the clinical presentation.

Lynch Syndrome and Colorectal Cancer Genetic Testing
The policy for Lynch syndrome genetic testing in CRC patients is based on an evidence report published by the Agency for Healthcare Research and Quality (AHRQ), a supplemental assessment to that report contracted by the EGAPP Working Group, and an EGAPP recommendation for genetic testing in CRC. Based on the AHRQ report and supplemental assessment, the EGAPP recommendation came to the following conclusions regarding genetic testing for MMR mutations 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 mutation testing and should not be used as a sole determinant or screening test.
- MSI and IHC screening tests for MMR mutations have similar sensitivity and specificity. MSI screening has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6 and a specificity of about 90% for all. It is likely that, using high-quality MSI testing methods, these parameters can be improved. Immunohistochemical screening has a sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for all.
- 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 mutations.
- A chain of indirect evidence can be constructed for the clinical utility of testing all patients with CRC for MMR mutations.
  1. The chain of indirect evidence from well-designed experimental nonrandomized studies (as noted below) 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 mutation.
  2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. About half of relatives received counseling, and 95% of these chose MMR gene mutation testing. Among those positive for
MMR gene mutations, uptake of colonoscopic surveillance beginning at age 20–25 years was high at 53–100%.

- One long-term, nonrandomized controlled study and one cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance vs. those who did not.
- Surveillance, prevention for other Lynch syndrome cancers (for detail, refer to last outline bullet)

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

- Subtotal colectomy is recommended as an alternative to segmental resection, but has not been shown superior in follow-up studies
- Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.
- Surveillance, prevention for other Lynch syndrome cancers:
  - While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In one retrospective study, women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer
  - In one study, surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown. Transvaginal ultrasound (TVUS) is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, TVUS in conjunction with endometrial biopsy has been recommended for surveillance.
  - Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supportive evidence.

Based on an indirect chain of evidence with adequate evidence of benefit to unaffected family members found to have Lynch syndrome, the EGAPP working group recommended testing all patients with CRC for MMR gene mutations. Further support for universal testing of CRC patients for MMR gene mutations was reported by Moreira and colleagues in 2013 in a comparison of universal testing of CRC patients to alternate screening approaches. The alternate screening approaches included using the Bethesda guidelines, the Jerusalem recommendations and a selective strategy including only those diagnosed with CRC before age 70, or after age 70 if meeting the Bethesda guidelines. In the analysis of 10,206 newly diagnosed CRC patients from 4 large cohort studies, MSI testing was used in 2,150 patients and immunostaining was used in 2,278 patients while both MSI and immunostaining were used in 5,591 patients. MMR gene mutations were found in 312 (3.1%) patients overall. The universal screening approach
was found to be superior to the other screening approaches in the population-based cohorts (n = 3671 probands) with a sensitivity of 100% (95% confidence interval [CI]: 99.3-100%), specificity of 93% (95% CI: 92.0-93.7%) and diagnostic yield of 2.2% (95% CI: 1.7-2.7%). The Bethesda guidelines screening sensitivity was 87.8% (95% CI: 78.9-93.2%) with a specificity of 97.5% (95% CI: 96.9-98.0%) and a diagnostic yield of 2.0% (95% CI: 1.5-2.4%; p < 0.001). The screening sensitivity with the Jerusalem recommendations was 85.4% (95% CI: 77.1-93.6%) with a specificity of 96.7% (95% CI: 96.0-97.2%) and a diagnostic yield of 1.9% (95% CI: 1.4-2.3%; p < 0.001). The selective strategy had a sensitivity of 95.1% (95% CI: 89.8-99.0%) with a specificity of 96.7% (95% CI: 96.0-97.2%) and a diagnostic yield of 1.9% (95% CI: 1.6-2.6%; p < 0.001). However, the diagnostic yield differences between the screening approaches were small, and the false-positive yield was 2.5% with universal screening. Whereas, in the selective strategy, 34.8% fewer patients required tumor MMR testing and 28.6% fewer analyses of MMR mutations resulting in 4.9% missed Lynch syndrome cases.

In addition to DNA MMR gene mutation testing, evidence now supports testing for EPCAM deletions in particular cases where all MMR gene mutation testing is negative, but tumor MSH2 IHC indicates lack of expression, and tumor MSI testing shows a high level of instability. The epithelial cell adhesion molecule 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 ribonucleic acid (mRNA) result in transcriptional ‘read-through’ and subsequent hypermethylation of the nearby and downstream MSH2 promoter. This hypermethylation prevents normal MSH2 protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an MSH2 mutation prevents MSH2 gene expression. Several studies have characterized such EPCAM deletions, established their correlation with the presence of EPCAM-MSH2 fusion mRNAs (apparently non-functional) and with the presence of MSH2 promoter hypermethylation, and, most importantly, have shown the co-segregation of these EPCAM mutations with Lynch-like disease in families. Because studies differ slightly in how patients were selected, prevalence of these EPCAM mutations is difficult to estimate but may be in the range of 20-40% of patients/families who meet Lynch syndrome criteria, do not have an MMR mutation, but have MSI-high tumor tissue. Kempers et al. reported that carriers of an EPCAM deletion had a 75% (95% CI: 65–85) cumulative risk of CRC by age 70 years, not significantly different from that of carriers of an MSH2 deletion (77% 64–90); mean age at diagnosis was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI: 0–27) by age 70, compared to carriers of a mutation in MSH2 (51% [95% CI: 33–69], p<0.001).

Grandval et al. selected 25 patients with tumors exhibiting complete loss of MSH2 protein but without a point mutation or genomic rearrangement of the MSH2 gene and found 7 cases of a deletion of the 3’ exon of EPCAM. Genetic testing was subsequently performed on 25 adult first-degree relatives of the 7 cases, and 12 relatives were found to be deletion carriers. Six additional relatives had deceased from Lynch-associated tumors, and 5 were obligate carriers. In summary, the risk to develop CRC was high, 93.1% (N = 27/29) in deletion carriers older than 30 years of age.

Although MMR gene sequencing of all patients is the most sensitive strategy, it is highly inefficient and cost-ineffective and not recommended. Rather, a screening strategy of MSI or IHC testing (with or without optional BRAF testing) is recommended and retains a relatively high sensitivity. Some evidence suggests
that IHC requires particular training and experience. Although a particular strategy was not recommended by the EGAPP Working Group, several are potentially effective; efficiency and cost-effectiveness may depend upon local factors.

In 2010, Bouzourene and colleagues analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC and 16 patients with Lynch syndrome. **BRAF** mutation 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** mutation, and all 11 patients were MLH1 methylated, suggesting patients with **BRAF** mutations could be excluded from germline testing for Lynch syndrome. In 2013, Jin et al. evaluated MMR proteins in 412 newly diagnosed CRC patients. MLH1 and PMS2 protein stains were absent in 65 (72%) patients who were subsequently tested for **BRAF** mutation. Thirty-six (55%) patients were found to have the **BRAF V600E** mutation, thus eliminating the need for further genetic testing or counseling for Lynch syndrome.

In 2013, Capper et al. reported on a technique of VE1 IHC testing for **BRAF** mutations on a series of 91 MSI-H CRC patients. The authors detected **BRAF**-mutated CRC with 100% sensitivity and 98.8% specificity. VE1 positive lesions were detected in 21% of **MLH1**-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore, VE1 IHC testing for **BRAF** could be an alternative to **MLH1** promoter methylation analysis.

To summarize, **BRAF** mutation **V600E** or **MLH1** promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH protein expression by IHC testing for **MLH1**. 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 mutation analysis for a Lynch syndrome diagnosis.

Previous recommendations have used family history as an initial screen to determine who should proceed further to MMR laboratory testing. Family history is important for counseling families, but based on this and similar evidence, it is not recommended as an initial screening tool to make decisions about testing patients who already have CRC. Recent studies have shown that limiting laboratory testing to patients who met even the more sensitive Revised Bethesda criteria (i.e., compared to the Amsterdam II criteria) would miss as much as 28% of Lynch syndrome cases. However, as noted in the policy statement, the Amsterdam II or Revised Bethesda criteria may be used in identifying those without CRC who might be tested.

Limiting testing for Lynch Syndrome on the basis of age (e.g., test only patients younger than age 50 years) is also not recommended. For example, Hampel et al. found that among 18 Lynch syndrome patients discovered among 500 unselected CRC patients, only 8 (44%) patients were diagnosed at age younger than 50 years. Similarly, Canard et al. reported that restricting screening to patients younger than 50 years would have missed about half of patients eventually found to have Lynch syndrome. Another group screened CRC patients who were younger than age 60 and identified 98 likely (MSI-positive, **BRAF**-negative) Lynch syndrome cases; of these, 47% were between ages 50 and 60 years. A large study of Lynch syndrome family studies found that the cumulative risk of CRC in MMR mutation carriers was only
13% (95% CI: 9-19) by age 50, but 35% (95% CI: 25-49%) by age 70. For \textit{MSH6} mutation carriers, however, CRC risks do not appear to increase until after age 60.

The estimated risk of stomach cancer in a large study of Lynch syndrome families was 6% (95% CI: 0.2-17%) for carriers of \textit{MLH1} mutations and warrants further study to address the utility of gastric surveillance.

As the EGAPP recommendations noted, the evidence to date is limited to clearly support benefit from genetic testing to the index patient with CRC if found to have Lynch syndrome. However, professional societies have reviewed the evidence and concluded that genetic testing likely has direct benefits for at least some patients with CRC and Lynch syndrome on the basis of differing recommendations for postsurgical surveillance, and for those who choose prophylactic surgical treatment instead of surveillance.

In the absence of preventive surgery, heightened surveillance is recommended. The National Comprehensive Cancer Network (NCCN) guidelines for colon cancer and for CRC screening recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year post-surgery and, if normal, again in years, then every year based on findings. However, for Lynch syndrome patients, colonoscopy is recommended every 1 to 2 years throughout life based on the high likelihood of cancer for patients diagnosed with Lynch syndrome prior to a cancer diagnosis, and on the high likelihood of a second primary cancer in those diagnosed with Lynch syndrome based on a first cancer diagnosis. For \textit{MLH1} and \textit{MSH2} mutation carriers, the NCCN guidelines indicate surveillance with colonoscopy should begin “at age 20-25 years or 2-5 years prior to the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1-2 years.” \textit{MSH6} mutation carriers should begin surveillance with colonoscopy “at age 30-35 years (may need to be earlier in some families, depending on ages of cancers observed) every 2-3 years and then after age 40 years every 1-2 years. \textit{PMS2} mutation carriers should begin surveillance with colonoscopy “at age 35-40 years (may need to be earlier in some families, depending on ages of cancers observed) every 2-3 years and then after age 50 years every 1-2 years. “If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered.”

Early documentation of the natural history of CRC in highly selected families with a strong history of hereditary CRC indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, in patients who already had CRC. As a result, in 1996, the Cancer Genetic Studies Consortium, a temporary National Institutes of Health (NIH)-appointed body, recommended that if CRC is diagnosed in patients with an identified mutation or a strong family history, a subtotal colectomy with ileorectal anastomosis (IRA) should be considered in preference to segmental resection. Although the average risk of a second primary is now estimated to be somewhat lower overall (see Description) in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. One study suggested that subtotal colectomy with IRA markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance. A mathematical model comparing total colectomy and IRA to hemicolectomy resulted in increased life expectancies of 2.3, 1, and 0.3 years for ages 27, 47, and 67, respectively; for Duke’s A, life expectancies for the same ages are 3.4, 1.5, and 0.4, respectively. Based on this work, the joint American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) review of risk-reducing surgery in hereditary cancers recommends offering both options to the patient with Lynch syndrome and CRC, especially those who are younger. This
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ASCO/SSO review also recommends 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.

Lynch Syndrome and Endometrial Cancer Genetic Testing
Several groups have recommended screening endometrial cancer patients for Lynch syndrome. At the 2010 Jerusalem Workshop on Lynch Syndrome, it was proposed that all incident cases of endometrial cancer be screened for Lynch syndrome using mismatch repair-immunohistochemical (MMR-IHC) testing. Clarke and Cooper note that Sloan-Kettering Cancer Center screens all patients younger than 50 years of age with endometrial cancer using MMR-IHC; as well as patients older than 50 years with suggestive tumor morphology, lower uterine segment (LUS) location, personal/family history, or synchronous cell carcinoma of the ovary. Kwon et al. recommended MMR-IHC screening of women with endometrial cancer at any age with at least one first-degree relative with a Lynch syndrome-associated cancer.

The risk of endometrial cancer in MMR mutation carriers has been estimated at 34% (95% CI: 17-60%) by age 70, and of ovarian cancer 8% (95% CI: 2-39%) by age 70. Risks do not appear to appreciably increase until after age 40.

In a recent prospective study, 179 consecutive endometrial cancer patients ≤70 years of age were analyzed for MSI, by IHC for expression of 4 MMR proteins, MMR gene methylation status and BRAF mutations. Results are presented in Table 1 below; 92% of patients were older than 50 years of age.

Table 1. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome

<table>
<thead>
<tr>
<th>Result</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>Mutation-positive</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No mutation found</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Refuses further DNA testing</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

H: high; MSI: microsatellite instability

Another study examined 625 endometrial cancer patients who underwent hysterectomy; endometrial cancer was classified as LUS in 9 patients. Twenty-seven randomly chosen patients from the non-LUS group were compared to the LUS group, and no statistically significant differences were found between groups with regard to MSI status or IHC findings. The incidence of Lynch syndrome in the LUS group was 1 in 9.

Kwon et al. 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 at any age, in women with at least one first-degree relative (FDR) with a Lynch-associated cancer, was the most cost-effective strategy (incremental cost-effectiveness ratio [ICER] = $9,126) 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 one FDR with a Lynch-associated cancer. Results are presented in Table 2:

Table 2. 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.

Female patients with Lynch syndrome who choose risk-reducing surgery are also encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. As already noted, in one retrospective study, women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer. In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome. This study also estimated that for every 100 women diagnosed with Lynch syndrome-associated CRC, about 23 will be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Recent data on mutation-specific risks suggest that prophylactic gynecological surgery benefits for carriers of \( MSH6 \) mutations may offer less obvious benefits compared to harms, as lifetime risk of endometrial cancer is lower than for carriers of \( MLH1 \) or \( MSH2 \) mutations, and lifetime risk of ovarian cancer is similar to the risk for the general population.

However, in the case of \( EPCAM \) deletion carriers, 3 recent studies found 3 cases of endometrial cancer in 103 female carriers who did not undergo preventative hysterectomy. Women with \( EPCAM \) deletions consequently have a lifetime risk of developing endometrial cancer decreased by 10-fold when compared to \( MMR \) gene-mutation carriers. This might support a clinical management scenario rather than prophylactic surgery. An alternative to prophylactic surgery is surveillance for endometrial cancer using TVUS and endometrial biopsy. Evidence indicates that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet indicates surveillance reduces mortality due to endometrial cancer. Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.

Ongoing Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
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</table>

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Summary

The evidence for genetic testing for the APC mutations in individuals who have a clinical differential of attenuated FAP, MAP, and Lynch syndrome, or at-risk relatives of patients with FAP includes a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. For patients with an APC mutation, 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 mutations in the \textit{MUTYH} gene. Testing for this genetic mutation 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 quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for \textit{MMR} mutations in (1) individuals who have a clinical differential diagnosis of attenuated FAP, MAP, and Lynch syndrome, or (2) individuals who have colon cancer, or (3) individuals who have endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, or (4) individuals who are at-risk relatives of patients with Lynch syndrome, or (5) patients without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria 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 (EGAPP) Working Group, and an EGAPP recommendation for genetic testing in CRC. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A chain of indirect 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 mutation, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and 1 cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed and did not follow recommended colonic surveillance. A positive genetic test for an MMR mutation can also lead to...
changes in management of other Lynch syndrome malignancies. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

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

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

\textbf{Practice Guidelines and Position Statements}

The NCCN guidelines for CRC screening recommend 2 approaches to Lynch syndrome mutation screening of either: (1) all CRCs or (2) CRC patients diagnosed before age 70 and those ages 70 and older when meeting Bethesda guidelines. Additionally, the CRC screening guidelines also recommend screening for Lynch syndrome for all endometrial cancer patients younger than 50 years-old. These guidelines note immunohistochemistry and sometimes MSI testing may be performed at some centers on all newly diagnosed colorectal and endometrial cancer patients to determine need for genetic testing for Lynch syndrome mutations regardless of family history. The guideline does not specifically mention \textit{EPCAM} deletion testing but does indicate that individuals with loss of \textit{MSH2} and/or \textit{MSH6} protein expression by immunohistochemistry, regardless of germline \textit{MMR} mutation status, should be followed as though they have Lynch syndrome. Genetic testing is recommended for at-risk family members of patients with positive mutations in\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, or \textit{PMS2}. The NCCN colon cancer screening guidelines also indicate \textit{BRAF} V600E testing or \textit{MLH1} promoter methylation testing may be used when \textit{MLH1} is not expressed in the tumor on IHC analysis to exclude a diagnosis of Lynch syndrome. As noted in the NCCN guidelines, "the presence of a \textit{BRAF} mutation indicates \textit{MLH1} expression is downregulated by somatic methylation of the promoter region of the gene and not by germline mutation." These guidelines also address FAP (classical and attenuated), and MAP, consistent with the information in this policy.

NCCN guidelines for colon cancer recommend colon cancer patients 70 years or younger plus those older than 70 years of age who meet the Bethesda guidelines be tested for the \textit{MMR} protein for possible Lynch syndrome. The colon cancer 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 on uterine neoplasms indicate all endometrial cancer patients, especially those younger than 50 years, should be considered for testing for genetic mutations such as Lynch syndrome.

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

Lynch syndrome (LS)
- "All newly diagnosed colorectal cancers should be evaluated for mismatch repair deficiency.
- "Analysis may be done by immunohistochemical (IHC) testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability; tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation.
- "Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF mutation or hypermethylation of MLH1), a known family mutation associated with LS, or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.
- "Genetic testing of patients with suspected LS should include germline mutation genetic testing for the MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes or the altered gene(s) indicated by IHC testing."

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

The European Society for Medical Oncology (ESMO) published clinical practice guidelines for familial CRC risk in 2010. These guidelines addressed Lynch syndrome, FAP, and MAP. No specific recommendations were made regarding how to initially identify Lynch syndrome cases; several methods, including clinical criteria and universal screening of all CRC cases, were mentioned. Other ESMO recommendations are consistent with the information in this policy.

The ASCO and the SSO recommends offering prophylactic total abdominal hysterectomy to female patients with CRC who have completed childbearing or to women undergoing abdominal surgery for other conditions, especially when there is a family history of endometrial cancer. This recommendation is based on the high rate of endometrial cancer in mutation-positive individuals and the lack of efficacy of screening.
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04/05/2006 Medical Director review
04/19/2006 Medical Policy Committee review
06/13/2007 Medical Director review
06/20/2007 Medical Policy Committee approval. Added statement to consider investigational when patient selection criteria are not met.
10/10/2007 Medical Director review
10/17/2007 Medical Policy Committee approval. No change to policy statement.
10/01/2008 Medical Director review
10/22/2008 Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009 Medical Director review
10/14/2009 Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010 Medical Policy Committee review
10/20/2010 Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/06/2011 Medical Policy Committee review
10/19/2011 Medical Policy Implementation Committee approval. Policy revised extensively to track BCBSA.
11/01/2012 Medical Policy Committee review
01/23/2013 Coding updated
01/09/2014 Medical Policy Committee review
01/15/2014 Medical Policy Implementation Committee approval. Policy title revised from “Genetic Testing for Inherited Susceptibility to Colon Cancer Including Microsatellite Instability Testing” to “Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes” since Lynch syndrome is not a polyposis syndrome. Added that BRAF V600E or MLH1 promoter methylation may be considered eligible for coverage when MLH1 is not expressed in the tumor on IHC analysis. Added that testing for all other gene mutations for Lynch syndrome or colorectal cancer is considered investigational.
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05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. Added the words “a patient with” to the guidelines.
04/02/2015 Medical Policy Committee review
04/20/2015 Medical Policy Implementation Committee approval. Bethesda Guidelines clarified. Added to eligibility statement for MMR gene mutation testing “Patients with ≥5% risk of Lynch Syndrome on one of the following mutation prediction models: MMRpro, PREMM1,2,6, or MMRpredict.”
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016 Coding update
04/07/2016 Medical Policy Committee review
04/20/2016 Medical Policy Implementation Committee approval. No changes to coverage eligibility.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. No changes to coverage eligibility.
Next Scheduled Review Date: 04/2018

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A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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