**Title:** Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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<td>Individuals: • With differential of attenuated FAP, MAP, and Lynch syndrome</td>
<td>Interventions of interest are: • Genetic testing for MUTYH gene mutations after a negative result for APC gene mutations</td>
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**DESCRIPTION**

Genetic testing is available for both affected individuals, and those at risk for various types of hereditary cancer. This evidence review describes genetic testing for hereditary colorectal cancer (CRC) and polyposis syndromes, including familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC), MUTYH-associated polyposis (MAP), and Lynch syndrome–related endometrial cancer.

**Background**

There are currently 2 well-defined types of hereditary colorectal cancer, familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer or HNPPC). Lynch syndrome has been implicated in some endometrial cancers as well.

**FAP and Associated Variants**

FAP typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will go on to develop colorectal cancer. The mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP accounts for about 1% of colorectal cancer 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). FAP associated with these collective extraintestinal manifestations is sometimes referred to as Gardner syndrome. FAP may also be associated with central nervous system (CNS) tumors, referred to as Turcot syndrome.

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

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<td>Interventions of interest are: • Genetic testing for MMR gene mutations</td>
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<td>Individuals: • Who are at-risk relatives of patients with Lynch or family history meeting appropriate criteria, but do not have CRC</td>
<td>Interventions of interest are: • Genetic testing for MMR gene mutations</td>
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<td>Individuals: • Who warrant Lynch testing, screen negative on MMR testing, but positive for MSI and lack MSH2 protein expression</td>
<td>Interventions of interest are: • Genetic testing for EPCAM gene mutations</td>
<td>Comparators of interest are: • No genetic testing</td>
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<td>Individuals: • With CRC in whom MLH1 protein is not expressed on immunohistochemical analysis</td>
<td>Interventions of interest are: • Genetic testing for BRAF V600E or MLH1 promoter methylation</td>
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CRC: colorectal cancer; FAP: familial adenomatous polyposis; MAP: MUTYH-associated polyposis; MSI: microsatellite instability.
A subset of FAP patients may have attenuated FAP (AFAP), typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, colorectal cancer occurring at an average age of 50-55 years, but a high lifetime risk of colorectal cancer of about 70% by age 80. 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 MUTYH-associated polyposis (MAP). MAP occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH mutations are associated with a cumulative colorectal cancer risk of about 80% by age 70, whereas monoallelic MUTYH mutation-associated risk of colorectal cancer appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk colorectal cancer predisposition is autosomal recessive in contrast to FAP. When relatively few (ie, between 10 and 99) adenomas are present and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include APC, MUTYH if APC is negative for mutations, and screening for mutations associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary 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 attenuated FAP versus MAP versus 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 colorectal cancer and other malignancies as a result of an inherited mutation in a DNA mismatch repair (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 colorectal cancer 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 colorectal cancer 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 colorectal cancer 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, ie, 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 colorectal cancer (average age of colorectal cancer 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 attenuated FAP versus MUTYH-associated polyposis 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 patients should proceed to direct sequencing for MMR gene mutations. Available screening methods are microsatellite instability (MSI) testing or immunohistochemical (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 mismatch repair 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 microsatellite instability (MSI) and resulting in a 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. IHC 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 colorectal cancer; 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 colorectal cancer 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 colorectal cancer 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 colorectal cancer.
- Patients with a differential diagnosis of Lynch syndrome vs. attenuated FAP vs. MYH-associated polyposis.
- Lynch syndrome patients. Genetic testing of the proband with colorectal cancer 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. 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 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," ie, 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 colorectal cancer 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 cancer in women under 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.

**Regulatory Status**

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

I. Lynch syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer [HNPCC]):

A. Genetic testing for HNPCC (MLH1, MSH2, MSH6, PMS2 sequence analysis) is considered **medically necessary** when one of the following criteria are met:

1. Meets Amsterdam II criteria or revised Bethesda guidelines (see Policy Guidelines below); or
2. A first-* or second-degree** relative with an HNPCC mutation (genes MLH1, MSH2, MSH6, PMS2); or
3. Endometrial cancer 50 years of age or younger.

B. Microsatellite instability (MSI) testing or immunohistochemical (IHC) analysis of tumors may be considered **medically necessary** as an initial test in persons with colorectal or endometrial cancer in order to identify those persons who should proceed with HNPCC mutation analysis.

II. Familial Adenomatous Polyposis and associated variance:

A. Adenosis polyposis coli (APC) genetic testing:

Adenosis polyposis coli (APC) genetic testing is considered **medically necessary** for either of the following indications:

1. Greater than 10 colonic polyps; or
2. First-degree* relatives diagnosed with familial adenomatous polyposis (FAP) or with a documented APC mutation. The specific APC mutation should be identified in the affected first-degree relative with FAP prior to testing the member, if feasible. Full sequence APC genetic testing is considered medically necessary only when it is not possible to determine the family mutation first.

APC genetic testing is considered **experimental / investigational** for all other indications.

B. MYH-Associated Polyposis (MAP) Genetic Testing:

Testing for MYH mutations is considered **medically necessary** for any of the following indications:

1. Personal history of 10 to 20 adenomatous polyposis who have negative APC mutation testing and a negative family history for adenomatous polyposis; OR
2. Personal history of 10 to 20 adenomatous polyposis whose family history is consistent with recessive inheritance (i.e., family history is positive only for sibling[s]); OR

3. Asymptomatic siblings of individuals with known MYH polyposis.

*First-degree relatives are parents, siblings, and offspring.
**Second-degree relatives are aunts, uncles, grandparents, niece, nephews or half-siblings.

Hereditary nonpolyposis colorectal cancer (HNPCC)-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome.

**Policy Guidelines**

1. 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.

2. 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.

3. In many cases, genetic testing for MUTYH gene mutations should first target the specific mutations Y165C and G382D, which account 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.

4. For patients with colorectal cancer being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test, or the immunohistochemistry (IHC) test with or without BRAF gene 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. IHC 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.

5. 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.

6. 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 32 U.S.-located laboratories that offer this service. In at least 1 laboratory, Lynch syndrome mutation testing is packaged under 1 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). Individualized testing (eg, targeted testing for a family mutation) can also be requested. The COLARIS® PLUS test includes full sequence analysis of MLH1, MSH2, MSH6, PMS2, and MYH genes and rearrangement analysis of MLH1, MSH2, MSH6, MYH, and EPCAM by microarray comparative genomic hybridization analysis, and multiplex ligation-dependent probe amplification analysis for PMS2.

7. 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.

8. 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):
   a. 3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis);
   b. 1 should be a first-degree relative of the other 2;
   c. 2 or more successive generations affected;
   d. 1 or more relatives diagnosed before the age of 50 years;
   e. Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma;
   f. Tumors should be verified by pathologic examination.
   g. Modifications:
      1) EITHER: very small families, which cannot be further expanded, can be considered to have HNPCC with only 2 colorectal cancers in first-degree relatives if at least 2 generations have the cancer and at least 1 case of colorectal cancer was diagnosed by the age of 55 years; OR
      2) in families with 2 first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

9. Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines).(Umar et al, 2004) The Bethesda guidelines are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also felt to be more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:
a. Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old;
b. Presence of synchronous (at the same time) or metachronous (at another time, ie, a recurrence of) CRC or other Lynch syndrome–associated tumors, regardless of age;
c. CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old;
d. CRC diagnosed in 1 or more first-degree relatives with a Lynch syndrome–associated tumor, with one of the cancers being diagnosed at younger than 50 years of age;
e. CRC diagnosed with 1 or more first-degree relatives with an HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed at younger than age 50 years, OR-CRC diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumor, regardless of age. (Lipton et al, 2004)

10. 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.

RATIONALE
The most recent literature review was performed through December 29, 2015. The following is a summary of the key findings to date.

Familial Adenomatous Polyposis Genetic Testing
The evidence review for familial adenomatous polyposis (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.
- 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 adenomatous polyposis coli (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 information on attenuated FAP and on MUTYH-associated polyposis (MAP) diagnostic criteria and genetic testing is based on information from GeneReviews\textsuperscript{16} and from several publications\textsuperscript{17-20} that build on prior, cited research. In addition, GeneReviews\textsuperscript{16} 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, ie, testing for FAP, is considered not necessary in those with classical FAP, because the genetic testing is not needed to make the diagnosis of FAP in these patients. Testing for the APC mutation has no role 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 evidence review for Lynch syndrome genetic testing in colorectal cancer (CRC) patients is based on an evidence report published by the Agency for Healthcare Research and Quality (AHRQ),\textsuperscript{21} a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group,\textsuperscript{9} and an EGAPP recommendation for genetic testing in CRC.\textsuperscript{22} 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 [microsatellite instability] and IHC [immunohistochemical] 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. IHC 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 colorectal cancer 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%.
    a. One long-term, nonrandomized controlled study and one cohort study of Lynch syndrome family members found significant reductions in colorectal cancer among those who followed recommended colonic surveillance vs. those who did not.
    b. Surveillance, prevention for other Lynch syndrome cancers (for detail, refer to 3c)
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 (ie, cancer index patient).
   a. Subtotal colectomy is recommended as an alternative to segmental resection, but has not been shown superior in follow-up studies.
   b. 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.
   c. Surveillance, prevention for other Lynch syndrome cancers:
      o 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.
      o 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.
      o 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 et al 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 2150 patients and immunostaining was used in 2278 patients, while both MSI and immunostaining were used in 5591 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% to 100%), specificity of 93% (95% CI, 92.0% to 93.7%) and diagnostic yield of 2.2% (95% CI, 1.7% to 2.7%). The Bethesda guidelines screening sensitivity was 87.8% (95% CI, 78.9% to 93.2%) with a specificity of 97.5% (95% CI, 96.9 to 98.0%) and a diagnostic yield of 2.0% (95% CI, 1.5% to 2.4%; p<0.001). The screening sensitivity with the Jerusalem recommendations was 85.4% (95% CI, 77.1% to 93.6%) with a specificity of 96.7% (95% CI, 96.0% to 97.2%) and a diagnostic yield of 1.9% (95% CI, 1.4% to 2.3%; p<0.001). The selective strategy had a sensitivity of 95.1% (95% CI, 89.8% to 99.0%) with a specificity of 95.5% (95% CI, 94.7% to 96.1%) and a diagnostic yield of 2.1% (95% CI, 1.6% to 2.6%; p<0.001). However, the diagnostic yield differences between the screening approaches were small, and the false positive yield was 2.5% with universal screening. 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 mismatch repair (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. 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 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 messenger RNAs (apparently nonfunctional) and with the presence of MSH2 promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM mutations with Lynch-like disease in families.14,24-28 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% to 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 to 85) cumulative risk of CRC by age 70 years, not significantly different from that of carriers of an MSH2 deletion (77%; 95% CI, 64 to 90); mean age at diagnosis was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0 to 27) by age 70, compared with carriers of a mutation in MSH2 (51%; 95% CI, 33 to 69; p<0.001).29

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 prime 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% (27/29) in deletion carriers older than 30 years of age.30

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.31 Although a particular strategy was not recommended by the EGAPP Working Group, several are potentially effective; efficiency and costeffectiveness may depend on local factors.

In 2010, Bouzourene et al analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC and 16 patients with Lynch syndrome.10 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.32 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 (ie, compared with 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 colorectal cancer who might be tested.

Limiting testing for Lynch syndrome on the basis of age (eg, test only patients <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 50 and 60 years of age. 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 to 19) by age 50, but 35% (95% CI, 25 to 49) by age 70. For 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 to 17%) for carriers of 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 postsurgery and, if normal, again in 3 years, then every 5 years 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 before 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. NCCN guidelines on Genetic/Familial High-Risk Assessment: Colorectal indicate for MLH1, MSH2, and EPCAM mutation carriers, 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 mutation 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 mutation 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.”

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–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 hemicolecystomy 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 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\textsuperscript{49} recommended MMR-IHC screening of women with endometrial cancer at any age with at least 1 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% to 60%) by age 70, and of ovarian cancer 8% (95% CI, 2 to 39) by age 70.\textsuperscript{4} 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 or younger 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; 92% of patients were older than 50 years of age.\textsuperscript{50}

<table>
<thead>
<tr>
<th>Table 1. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome</th>
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<tbody>
<tr>
<td><strong>Result</strong></td>
</tr>
<tr>
<td>Stable MMS and normal protein staining</td>
</tr>
<tr>
<td>MSI-H and MLH1 absent</td>
</tr>
<tr>
<td>Sporadic MSI-H</td>
</tr>
<tr>
<td>Likely to have Lynch syndrome</td>
</tr>
<tr>
<td>Mutation-positive</td>
</tr>
<tr>
<td>No mutation found</td>
</tr>
<tr>
<td>Refuses further DNA testing</td>
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</tbody>
</table>

MSI: microsatellite instability.

Another study examined 625 endometrial cancer patients who underwent hysterectomy; endometrial cancer was classified as LUS in 9 patients.\textsuperscript{51} Twenty-seven randomly chosen patients from the non-LUS group were compared with 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.\textsuperscript{52,53}

Kwon et al\textsuperscript{49} 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 1 first-degree relative with a Lynch-associated cancer, was the most cost-effective strategy (incremental cost-effectiveness ratio, $9126) for identifying Lynch syndrome and subsequent CRC cases. The model used published prevalence estimates of Lynch syndrome in all endometrial cancer patients of 2% (range, 1%-3%), and of 17% (range, 15%-20%) in endometrial cancer patients with at least 1 first-degree relative with a Lynch-associated cancer. Results are presented in Table 2.

<table>
<thead>
<tr>
<th>TABLE 2. Modeling of Endometrial Cancer Patient Screening Strategies for Detecting Lynch Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing Strategy</strong></td>
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<tr>
<td>Amsterdam II criteria</td>
</tr>
<tr>
<td>Age &gt;50 y, and at least 1 FDR (Lynch-associated cancer)</td>
</tr>
<tr>
<td>IHC triage &lt;age 50 y</td>
</tr>
<tr>
<td>IHC triage &lt;age 60 y</td>
</tr>
<tr>
<td>IHC triage at any age; at least 1 FDR with Lynch-associated cancer</td>
</tr>
<tr>
<td>IHC triage all endometrial cancers</td>
</tr>
</tbody>
</table>

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 1 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 gynecologic surgery benefits for carriers of MSH6 mutations may offer less obvious benefits compared with 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 with 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 and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 3.

<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>
<td></td>
</tr>
<tr>
<td>NCT01447199</td>
<td>The Molecular Predisposition to Hereditary Nonpolyposis Colon Cancer (HNPCC)</td>
<td>2000</td>
<td>Sep 2017</td>
</tr>
<tr>
<td>NCT01850654</td>
<td>Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome</td>
<td>4000</td>
<td>Sep 2017</td>
</tr>
</tbody>
</table>

| Unpublished       |                                                               |                    |                 |
| NCT01646112       | Living in Lynch Syndrome Limbo: Exploring the Meaning of Uncertain Genetic Test Results | 40                 | Completed       |

NCT: national clinical trial.

**Summary of Evidence**
The evidence for genetic testing for the adenomatous polyposis coli (APC) mutation in individuals with a clinical differential diagnosis of attenuated familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), and Lynch syndrome, or individuals who are at-risk relatives of patients with FAP, includes a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, as well as 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 MUTYH gene. Testing for this genetic mutation is necessary.
when the differential diagnosis includes both FAP and MAP, because distinguishing between the
two leads to different management strategies. In some cases, Lynch syndrome may be part of
the same differential diagnosis, depending on presentation. 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 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, 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, as well as 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 affect 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 recommended colonic surveillance
versus those who did not. 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 EPCAM mutations in individuals who have a CRC in which
MMR testing is negative for all MMR mutations but who screen positive for microsatellite
instability and lack MSH2 immunohistochemical evidence of protein expression includes mutation
prevalence studies and case series. Relevant outcomes are overall survival, disease-specific
survival, as well as test accuracy and validity. Studies have shown an association between EPCAM
mutations and Lynch-like disease in families and the cumulative risk for CRC is similar to carriers
of an MSH2 mutation. Identification of an EPCAM mutation could lead to changes in management
that lead to improved 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 BRAF V600E or MLH1 promoter methylation in individuals
who have CRC but in whom MLH1 protein is not expressed on immunohistochemical analysis
includes a few case series. Relevant outcomes are overall survival, disease-specific survival, as
well as test accuracy and validity. Studies have shown, with high sensitivity and specificity, an
association of BRAF V600E mutation or 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.
Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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

In response to requests, input was received through 3 physician specialty societies and 3 academic medical centers while this policy was under review for October 2009.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines for Genetic/Familial High-Risk Assessment41: Colorectal recommend 2 approaches to Lynch syndrome mutation screening of either: (1) all newly diagnosed colorectal and endometrial cancers 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. These guidelines note IHC 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 guidelines note “evidence has shown 3 deletions in the EPCAM gene, which lead to hypermethylation of the MSH2 promoter and subsequent MSH2 silencing, are an additional cause of Lynch syndrome.” Genetic testing is recommended for at-risk family members of patients with positive mutations in MLH1, MSH2, MSH6, or PMS2. The NCCN guidelines also indicate BRAF V600E testing or MLH1 promoter methylation testing may be used when 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 BRAF mutation indicates 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 evidence review.

NCCN guidelines for colon cancer recommend colon cancer patients 70 years or younger and those older than 70 years of age that meet the Bethesda guidelines be tested for the MMR protein for possible Lynch syndrome.38 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.58

American College of Gastroenterology

The American College of Gastroenterology (ACG) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.59

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.60

• “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.”

European Society for Medical Oncology
The European Society for Medical Oncology (ESMO) published clinical practice guidelines for familial CRC risk in 2010.2 These guidelines addressed Lynch syndrome, familial adenomatous polyposis, 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 evidence review.

American Society of Clinical Oncology and Society of Surgical Oncology
The American Society of Clinical Oncology and the Society of Surgical Oncology 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.46

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.
## CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

<table>
<thead>
<tr>
<th>CPT/HCPCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81210</td>
<td>BRAF (rB-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
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<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<tr>
<td>81301</td>
<td>Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
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<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
</tbody>
</table>
Genetic testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

- 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.

**ICD-9 Diagnoses**

152.0 Malignant neoplasm of small intestine, including duodenum, duodenum
152.1 Malignant neoplasm of small intestine, including duodenum, jejunum
152.2 Malignant neoplasm of small intestine, including duodenum, ileum
152.3 Malignant neoplasm of small intestine, including duodenum, Meckel’s diverticulum
152.8 Malignant neoplasm of small intestine, including duodenum, other specified sites of small intestine
152.9 Malignant neoplasm of small intestine, including duodenum, small intestine unspecified
153.0 Malignant neoplasm of colon, Hepatic flexure
153.1 Malignant neoplasm of colon, Transverse colon
153.2 Malignant neoplasm of colon, Descending colon
153.3 Malignant neoplasm of colon, Sigmoid colon
153.4 Malignant neoplasm of colon, Cecum
153.5 Malignant neoplasm of colon, Appendix
153.6 Malignant neoplasm of colon, Ascending colon
153.7 Malignant neoplasm of colon, Splenic flexure
153.8 Malignant neoplasm of colon, Other specified sites of large intestine
153.9 Malignant neoplasm of colon, Colon, unspecified
154.0 Malignant neoplasm of rectosigmoid junction
157.1 Malignant neoplasm of pancreas, body of pancreas
157.2 Malignant neoplasm of pancreas, tail of pancreas
183.0 Malignant neoplasm of ovary
183.2 Malignant neoplasm of ovary, fallopian tube
183.3 Malignant neoplasm of ovary, broad ligament
183.4 Malignant neoplasm of ovary, parametrium
183.5 Malignant neoplasm of ovary, round ligament
187.2 Malignant neoplasm of kidney and other and unspecified urinary organs, ureter
191.0 Malignant neoplasm of brain, cerebrum, except lobes and ventricles
191.1 Malignant neoplasm of brain, frontal lobe
191.2 Malignant neoplasm of brain, temporal lobe
191.3 Malignant neoplasm of brain, parietal lobe
191.4 Malignant neoplasm of brain, occipital lobe
191.5 Malignant neoplasm of brain, ventricles
191.6 Malignant neoplasm of brain, cerebellum NOS
191.7 Malignant neoplasm of brain, brain stem
191.8 Malignant neoplasm of brain, other parts of brain
191.9 Malignant neoplasm of brain, unspecified
211.3 Benign neoplasm of colon
211.4 Benign neoplasm of rectum and anal canal
230.3 Carcinoma in situ of colon
230.4 Carcinoma in situ of rectum (includes rectosigmoid junction)
V10.05 Personal history of malignant neoplasm of large intestine
V10.06 Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus
V16.0 Family history of malignant neoplasm of gastrointestinal tract
V26.3 Admission/Encounter for genetic counseling

**ICD-10 Diagnoses (Effective October 1, 2015)**

C17.0 Malignant neoplasm of duodenum
C17.1 Malignant neoplasm of jejunum
C17.2 Malignant neoplasm of ileum
C17.3 Meckel's diverticulum, malignant
C17.8 Malignant neoplasm of overlapping sites of small intestine
C17.9 Malignant neoplasm of small intestine, unspecified
C18.3 Malignant neoplasm of hepatic flexure
C18.4 Malignant neoplasm of transverse colon
C18.6 Malignant neoplasm of descending colon
C18.7 Malignant neoplasm of sigmoid colon
C18.0 Malignant neoplasm of cecum
C18.1 Malignant neoplasm of appendix
C18.2 Malignant neoplasm of ascending colon
C18.5 Malignant neoplasm of splenic flexure
C18.8 Malignant neoplasm of overlapping sites of colon
C18.9 Malignant neoplasm of colon, unspecified
C19 Malignant neoplasm of rectosigmoid junction
C25.1 Malignant neoplasm of body of pancreas
C25.2 Malignant neoplasm of tail of pancreas
C56.1 Malignant neoplasm of right ovary
C56.2 Malignant neoplasm of left ovary
C56.9 Malignant neoplasm of unspecified ovary
C57.00 Malignant neoplasm of unspecified fallopian tube
C57.01 Malignant neoplasm of right fallopian tube
C57.02 Malignant neoplasm of left fallopian tube
C57.10 Malignant neoplasm of unspecified broad ligament
C57.11 Malignant neoplasm of right broad ligament
C57.12 Malignant neoplasm of left broad ligament
C57.3 Malignant neoplasm of parametrium
C57.20  Malignant neoplasm of unspecified round ligament
C57.21  Malignant neoplasm of right round ligament
C57.22  Malignant neoplasm of left round ligament
C60.1   Malignant neoplasm of glans penis
C71.0   Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1   Malignant neoplasm of frontal lobe
C71.2   Malignant neoplasm of temporal lobe
C71.3   Malignant neoplasm of parietal lobe
C71.4   Malignant neoplasm of occipital lobe
C71.5   Malignant neoplasm of cerebral ventricle
C71.6   Malignant neoplasm of cerebellum
C71.7   Malignant neoplasm of brain stem
C71.8   Malignant neoplasm of overlapping sites of brain
C71.9   Malignant neoplasm of brain, unspecified
D12.0   Benign neoplasm of cecum
D12.1   Benign neoplasm of appendix
D12.2   Benign neoplasm of ascending colon
D12.3   Benign neoplasm of transverse colon
D12.4   Benign neoplasm of descending colon
D12.5   Benign neoplasm of sigmoid colon
D12.6   Benign neoplasm of colon, unspecified
K63.5   Polyp of colon
D12.7   Benign neoplasm of rectosigmoid junction
D12.8   Benign neoplasm of rectum
D12.9   Benign neoplasm of anus and anal canal
D01.0   Carcinoma in situ of colon
D01.1   Carcinoma in situ of rectosigmoid junction
D01.2   Carcinoma in situ of rectum
Z85.038 Personal history of other malignant neoplasm of large intestine
Z85.048 Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z80.0   Family history of malignant neoplasm of digestive organs

**REVISIONS**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>05-13-2011</td>
<td>Policy added to the bcbsks.com web site.</td>
</tr>
</tbody>
</table>
| 01-01-2012 | In the Coding section:
|            |   ▪ Added the new codes: 81210, 81292-81301                                                     |
| 04-10-2012 | In the Coding section:
|            |   ▪ Replaced Diagnosis code 183.1 with correct code 183.2.                                     |
|            |   ▪ Removed HCPCS codes: S3828, S3829, S3830, S3831 (Deleted codes, effective April 1, 2012.) |
| 01-15-2013 | In the Coding section:
|            |   ▪ Added CPT codes: 81401, 81406                                                               |
|            |   ▪ Added new CPT codes: 81201, 81202, 81203(Effective 01-01-2013)                             |
|            |   ▪ Removed CPT codes:83890, 83892, 83898, 83902, 83904, 83905, 83906, 83912 (Effective 12-31-2012) |
| 03-26-2013 | Updated Description section.                                                                     |
|            | In Policy section:                                                                             |
- In Item I, Note, Amsterdam II Criteria, added "6. Modifications: EITHER: very small families, which cannot be further expanded, can be considered to have HNPCC with only 2 colorectal cancers in first-degree relatives if at least two generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years; OR: in families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient."

- In Item I, Note, Revised Bethesda Criteria, added "6. Colorectal cancer diagnosed with one or more first-degree relatives with HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous bland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed under age 50 years, OR colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC related tumor, regardless of age. (15)"

Updated Rationale section.

Updated Reference section.

08-21-2013  In Coding section:
- Removed CPT code 81210.
- Added ICD-10 Diagnosis codes *(Effective October 1, 2014)*

01-01-2015  Policy posted 01-16-2015

In Coding section:
- Added CPT Code: 81288 *(Effective January 1, 2015)*

03-18-2015  In Title section:
- Changed title name from "Genetic Testing for Inherited Susceptibility to Colon Cancer, Including Microsatellite Instability Testing"

Updated Description section.

In Policy section:
- Removed Amsterdam II criteria and Revised Bethesda guidelines.
- In Policy Guidelines, added items 6-9.

Updated Rationale section.

In Coding section:
- Added CPT Codes 81210, 81317, 81318, 81319, and 81403.
- Removed CPT Code 81406.

Updated References section.

01-01-2016  In Coding section:
- Revised nomenclature to CPT codes: 81210 and 81401.

02-03-2016  Updated Description section.

In Policy section:
- Added statement on genetic counseling to Policy Guidelines.

Updated Rationale section.

Updated References section.

Added Appendix section.

05-25-2016  Updated Description section.

In Policy section:
- Revised Policy Guideline Item 6.

Updated Rationale section.

Updated References section.

11-09-2016  In Policy section:
- In Item I B, removed "when feasible" and "who meet the revised Bethesda criteria (see Policy Guidelines below)" and added "or immunohistochemical (IHC) analysis of
In Coding section:
- Added CPT codes: 88341, 88342, 88344.

REFERENCES


Other References:
1. Blue Cross and Blue Shield of Kansas Surgery Liaison, August 2010; August 2011.
## Appendix

**Appendix Table 1: Categories of Genetic Testing Addressed in This Policy**

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