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

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DESCRIPTION
Genetic testing is available for both affected individuals and those at risk for various types of hereditary cancer. This policy evaluates genetic testing for hereditary colorectal cancer and polyposis syndromes, including familial adenomatous polyposis, Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer [CRC]), MUTYH-associated polyposis, and Lynch syndrome-related endometrial cancer.

OBJECTIVE
The objective of this policy is to assess whether the use of genetic testing improves the net health outcome in patients with Lynch syndrome and other inherited colon cancer syndromes.

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

FAP and Associated Variants
FAP 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

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CRC: colorectal cancer; FAP: familial adenomatous polyposis; MAP: MUTYH-associated polyposis; MMR: mismatch repair; MSI: microsatellite instability.
Gardner syndrome. FAP may also be associated with central nervous system (CNS) tumors, referred to as Turcot syndrome.

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

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 variants; some of these patients instead have variants 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 variants are associated with a cumulative colorectal cancer risk of about 80% by age 70, whereas monallelic MUTYH variant-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 variants, and screening for variants associated with Lynch syndrome.

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

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

- Family members of patients with FAP and a known APC variant. Those without the specific variant 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
Lynch syndrome is an inherited disorder that results in a higher predisposition to CRC and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3% to 5% of all CRC. People with Lynch syndrome have a 70% to 80% lifetime risk of
developing any type of cancer.\textsuperscript{4,5} However the risk varies by genotype. It occurs as a result of germine variant in the mismatch repair (MMR) genes that include \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2}. In approximately 80\% of cases, the variants are located in the \textit{MLH1} and \textit{MSH2} genes, while 10\% to 12\% of variants are located in the \textit{MSH6} gene and 2\% to 3\% in the \textit{PMS2} gene. Also, variants in 3 additional genes (\textit{MLH3}, \textit{PMS1}, \textit{EX01}) have also been implicated with Lynch Syndrome. Notably, in individuals meeting the various clinical criteria for Lynch syndrome, 50\% individuals have a variant in the \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2} genes. The lifetime risk of CRC is nearly 80\% in individuals carrying a variant in one of these genes.

\textbf{Testing}

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

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

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

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

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

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

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

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

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

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

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

Population Selection
Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR variants, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria\(^{19}\) (low sensitivity but high specificity), Bethesda guidelines\(^{20}\) (better sensitivity but poorer specificity) and risk prediction models (eg, MMRpro; PREMM5; MMRpredict).\(^{21}\) While family history is an important risk factor and should not be discounted in counseling families, it has poor sensitivity and specificity for identifying Lynch syndrome. Based on this and other evidence, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing all newly diagnosed patients with CRC for Lynch syndrome, using a screening strategy based on MSI or IHC (with or without BRAF) followed by sequencing in screen-positive patients. This recommendation includes genetic testing for the following types of patients:

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

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 variant (genes MLH1, MSH2, MSH6, PMS2); or
3. Endometrial cancer 50 years of age or younger.
B. HNPCC genetic testing is considered experimental / investigational for all other indications.

C. 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 variant analysis.

D. MSI testing or IHC analysis of tumors is considered experimental / investigational for all other indications.

II. Familial Adenomatous Polyposis and associated variance:

A. 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 variant. The specific APC variant 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 variant first.

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

C. Testing for MYH variants is considered medically necessary for any of the following indications:
   1. Personal history of 10 to 20 adenomatous polyposis who have negative APC variant 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 (ie, family history is positive only for sibling[s]); OR
   3. Asymptomatic siblings of individuals with known MYH polyposis.

D. MAP genetic testing is considered experimental / investigational for all other indications.

*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 variant found in the affected family member.
3. In many cases, genetic testing for MUTYH gene variants should first target the
specific variants Y165C and G382D, which account more than 80% of variants 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 variant 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
variant, if any, and may also provide some additional information if MMR genetic
testing is inconclusive.
5. When indicated, genetic sequencing for MMR gene variants should begin with MLH1
and MSH2 genes unless otherwise directed by the results of IHC testing. Standard
sequencing methods will not detect large deletions or duplications; when MMR gene
variants are expected based on IHC or MSI studies but none are found by standard
sequencing, additional testing for large deletions or duplications is appropriate.
6. Several Clinical Laboratory Improvement Amendments (CLIA)–licensed clinical
laboratories offer MMR gene variant testing for Lynch syndrome. For example, the
GeneTests website (available online at:
tests) lists 32 U.S.-located laboratories that offer this service. In at least 1
laboratory, Lynch syndrome variant 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 variant) 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 variant testing and 14 that provide MUTYH variant 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 July 21, 2017. The following is a summary of the key findings to date.

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key findings to date.

Genetic Testing for Familial Adenomatous Polyposis and MUTYH-Associated Polyposis

Clinical Context and Test Purpose

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

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

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

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

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

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

Comparators
The comparator of interest is no genetic testing.

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

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

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

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

Analytic Validity
Limited relevant primary data on analytic validity were identified. The test is generally done by gene sequencing analysis, which is expected to have high analytic validity when performed under optimal conditions.
Clinical Validity

The evidence review for FAP genetic testing was originally informed by a 1998 TEC Assessment. The additional information on attenuated FAP and on MAP diagnostic criteria and genetic testing is based on information from GeneReviews and from several publications that build on prior, cited research.

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

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

Section Summary: Clinical Validity

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

Clinical Utility

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. Such information is not available.

Chain of Evidence

Genetic testing of at-risk relatives of patients with FAP and/or a known APC variant may have clinical utility:

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

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

The 1998 TEC Assessment\textsuperscript{22} offered the following conclusions:

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

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

Testing for the APC variant has no role in the evaluation, diagnosis, or treatment of patients with classical FAP where the diagnosis and treatment are based on the clinical presentation.

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<td>Vasen et al (1990)\textsuperscript{39}</td>
<td>Observational: CRC rate compared in 230 confirmed FAP cases; 104 symptomatic and 126 at-risk family members identified by screening</td>
<td>47% of symptomatic cases had CRC at a mean age of 35 y vs 4% at 24 y</td>
</tr>
<tr>
<td>Bjork et al (2000)\textsuperscript{40}</td>
<td>Observational: 195 confirmed cases of FAP underwent ileorectal anastomosis and followed for, on average, 14 y</td>
<td>Cumulative risk of rectal cancer mortality was 7% at 20 y postsurgery and cumulative mortality was 11.1% at the age of 70 y, indicating a substantial risk of developing cancer even after surgery</td>
</tr>
<tr>
<td>Järvinen (1992)\textsuperscript{41}</td>
<td>Observational: 251 individuals from 81 affected families; 76 individuals diagnosed during family screening compared with 116 symptomatic individuals with probands</td>
<td>65.5% of symptomatic cases had CRC vs 6.6% cases among those screened during family screening</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; FAP: familial adenomatous polyposis.

\textit{Section Summary: Clinical Utility}

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

\textbf{Lynch Syndrome and Colorectal Cancer Genetic Testing}

\textbf{Clinical Context and Test Purpose}

The purpose of genetic testing for Lynch syndrome is to

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

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

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

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

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

Comparators
The comparator of interest is no genetic testing.

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

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

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

Setting
Ordering and interpreting genetic testing may be complex and is best done by experienced specialists such as gastroenterologists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.
Analytic Validity
Limited relevant primary data on analytic validity were identified. The test is generally done by gene sequencing analysis, which is expected to have high analytic validity when performed under optimal conditions.

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

The evidence for Lynch syndrome genetic testing in patients with CRC is based on an evidence report published by the Agency for Healthcare Research and Quality (2007), a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009), and an EGAPP recommendation (2009) for genetic testing in CRC. Based on the Agency for Healthcare Research and Quality report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for MMR variants in patients already diagnosed with CRC:

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

Moreira et al (2012) reported the comparison of universal testing of CRC patients with alternative screening approaches. The alternative screening approaches included using the Bethesda guidelines, the Jerusalem recommendations, and a selective strategy including only those diagnosed with CRC before age 70, or after age 70 if meeting the Bethesda guidelines.

- In the analysis of 10,206 newly diagnosed CRC patients from 4 large cohort studies, MSI testing was used in 2150 patients, and immunostaining was used in 2278 patients, while both MSI and immunostaining were used in 5591 patients. MMR gene variants were found in 312 (3.1%) patients overall.
- The universal screening approach was superior to the other screening approaches in the population-based cohorts (n=3671 probands), with a sensitivity of 100% (95% confidence interval [CI], 99.3% to 100%), specificity of 93% (95% CI, 92.0% to 93.7%), and diagnostic yield of 2.2% (95% CI, 1.7% to 2.7%).
- The Bethesda guidelines screening sensitivity was 87.8% (95% CI, 78.9% to 93.2%), with a specificity of 97.5% (95% CI, 96.9% to 98.0%) and a diagnostic yield of 2.0% (95% CI, 1.5% to 2.4%; p<0.001).
- The screening sensitivity with the Jerusalem recommendations was 85.4% (95% CI, 77.1% to 93.6%), with a specificity of 96.7% (95% CI, 96.0% to 97.2%) and a diagnostic yield of 1.9% (95% CI, 1.4% to 2.3%; p<0.001).
- The selective strategy had a sensitivity of 95.1% (95% CI, 89.8% to 99.0%), with a specificity of 95.5% (95% CI, 94.7% to 96.1%) and a diagnostic yield of 2.1% (95% CI, 1.6% to 2.6%; p<0.001).
However, the diagnostic yield differences between the screening approaches were small, and the
false-positive yield was 2.5% with universal screening. In the selective strategy, 34.8% fewer
patients required tumor MMR testing and 28.6% fewer required analyses of MMR variants,
resulting in 4.9% missed Lynch syndrome cases.

Several studies have characterized EPCAM deletions, established their correlation with the
presence of EPCAM-MSH2 fusion messenger RNAs (apparently nonfunctional) and with the
presence of MSH2 promoter hypermethylation, and, most importantly, have shown the
cosegregation of these EPCAM variants with Lynch-like disease in families.11-16 Because studies
differ slightly in how patients were selected, the prevalence of these EPCAM variants is difficult to
estimate but may be in the range of 20% to 40% of patients/families who meet Lynch syndrome
criteria, do not have an MMR variant, but have MSI-high tumor tissue. Kempers et al (2011)
reported that carriers of an EPCAM deletion had a 75% (95% CI, 65% to 85%) cumulative risk of
CRC by age 70 years, which did not differ significantly from that of carriers of an MSH2 deletion
(77%; 95% CI, 64% to 90%); mean age at diagnosis was 43 years. However, the cumulative
risk of endometrial cancer was low at 12% (95% CI, 0% to 27%) by age 70 compared with
carriers of an MSH2 variant (51%; 95% CI, 33% to 69%; p<0.001).45

In 2010, Bouzourene et al analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC
and 16 patients with Lynch syndrome.10 BRAF variant was not found in any of the Lynch
syndrome patients. MLH1 promoter methylation was only present in 1 Lynch syndrome patient.
However, 8 of the 11 sporadic CRC patients had the BRAF variant, and all 11 patients were MLH1
methylated, suggesting patients with BRAF variants could be excluded from germline testing for
Lynch syndrome. In 2013, Jin et al evaluated MMR proteins in 412 newly diagnosed CRC
patients.46 MLH1 and PMS2 protein stains were absent in 65 patients who were subsequently
tested for BRAF variant. Thirty-six (55%) of the 65 patients had the BRAF V600E variant, thus
eliminating the need for further genetic testing or counseling for Lynch syndrome. In 2013,
Capper et al reported on a technique of V600E IHC testing for BRAF variants on a series of 91
stratified as high MSI CRC patients.47 The authors detected BRAF-mutated CRC with 100%
sensitivity and 98.8% specificity. V600E positive lesions were detected in 21% of MLH1-negative
CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore,
V600E IHC testing for BRAF could be an alternative to MLH1 promoter methylation analysis. To
summarize, BRAF V600E variant or MLH1 promoter methylation testing are optional screening
methods that may be used when IHC testing shows a loss of MLH protein expression. The
presence of BRAF V600E or absence of MLH1 protein expression due to MLH1 promoter
methylation rarely occurs in Lynch syndrome and would eliminate the need for further germline
variant analysis for a Lynch syndrome diagnosis.48

The risk of endometrial cancer in MMR variant carriers has been estimated at 34% (95% CI, 17%
to 60%) by age 70, and at 8% for ovarian cancer (95% CI, 2% to 39%) by age 70.49 Risks do
not appear to appreciably increase until after age 40. In a 2012 prospective study, 179
consecutive endometrial cancer patients 70 years of age or younger were analyzed for MSI, using
IHC for expression of 4 MMR proteins, MMR gene methylation status, and BRAF variants. Results
are presented in Table 2; 92% of patients were older than 50 years of age.50
Table 2. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome

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

H: high; MSI: microsatellite instability.

Clinical Utility

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. Such information is not available.

Chain of Evidence

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

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

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

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

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

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

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

1. The chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant.
2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. About half of relatives received counseling, and 95% of these chose MMR gene variant testing. Among those...
positive for MMR gene variants, uptake of colonoscopic surveillance beginning at age 20 to 25 years was high at 53% to 100%.
  - One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance vs those who did not.
  - Surveillance, prevention for other Lynch syndrome cancers.

3. The chain of evidence from descriptive studies and expert opinion is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (ie, 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 a retrospective study (2006), of 315 women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.58
    - In a 2010 study, surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown.10 Transvaginal ultrasound (TVUS) is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, TVUS in conjunction with endometrial biopsy has been recommended for surveillance.
    - Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supportive evidence.

Early documentation (1987) of the natural history of CRC in highly selected families with a strong history of hereditary CRC indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, in those with CRC.59 As a result, in 1997, the Cancer Genetic Studies Consortium recommended that if CRC is diagnosed in patients with an identified variant or a strong family history, a subtotal colectomy with ileorectal anastomosis should be considered as an option to segmental resection.60 Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. One 2003 study suggested that subtotal colectomy with ileorectal anastomosis markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance.61 A 2003 mathematical model comparing total colectomy plus ileorectal anastomosis with hemicolectomy estimated increased life expectancies of 2.3, 1, and 0.3 years for ages 27, 47, and 67, respectively; for stage I cancer, estimated life expectancies for the same ages were 3.4, 1.5, and 0.4, respectively.62 Based on this work, the 2006 joint American Society of Clinical Oncology and Society of Surgical Oncology review assessing risk-reducing surgery in hereditary cancers
recommended offering both options to patients with Lynch syndrome and CRC, especially those who are younger.63 The societies’ review also recommended offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch anal anastomosis or anterior proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

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

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
</table>
| Järvinen et al (1995)64      | Observational; 252 at-risk individuals from 20 of 22 families with MMR variants invited for colonoscopy screening every 3 y; 133 agreed; 118 declined. Of those who declined, 8 (15%) had screening examinations outside of the study. | • Screening vs nonscreening  
• Incidence of CRC: 4.5% (n=6) vs 11.9% (n=14) (p=0.03)  
• 6 vs 12 deaths within 10 y (p=0.08) |
| De Vos tot Nederveen Cappel et al (2002)66 | Observational; 857 at-risk individuals from 114 HNPCC- or MMR-positive families. | 10-y cumulative risk of CRC, 15.7% vs 3.4% for partial vs subtotal colectomy |
| Dove-E Edwin et al (2005)67   | Prospective observational; 554 individuals from 290 at-risk families with HNPCC or MMR variants followed for 16 y | Estimated 72% decrease in CRC death in screened individuals |
| Järvinen et al (2009)68      | Observational; 609 individuals from 57 LS families; 242 variant-positive and 367 variant-negative followed for cancer incidence over a mean of 11.5 y | No increase in cancer mortality in variant-positive vs -negative individuals; 74 variant-positive individuals had adenomas removed; 48 variant-positive women had prophylactic hysterectomy |
| Syngal et al (1998)69        | Decision analysis model: Assessed impact of decision about immediate prophylactic colectomy, delayed colectomy, or endoscopic surveillance at the time of a positive result on genetic testing | Compared with no intervention, all risk-reduction strategies led gains in life expectancy from 13.5 y for surveillance to 15.6 y for prophylactic proctocolectomy at 25 y of age. Also, surveillance led to QALY gain of 3.1 y vs 0.3 y with subtotal colectomy. |
| Engel et al (2010)70         | Prospective cohort: Assessed efficacy of annual colonoscopic surveillance in 1126 at-risk individuals from families with LS | 99 CRCs found in 90 individuals; 71 were diagnosed by surveillance colonoscopies. Median time between CRCs detected through follow-up colonoscopy and preceding colonoscopy was 11.3 mo. |
• Cross-sectional cohort: Examined adoption of risk-reduction strategies using a one-time questionnaire in 77 women at risk of LS-associated endometrial cancer | • In cross-sectional cohort, 58/77 (75%) women reported engaging in endometrial cancer risk-reduction  
• Proportion of women engaging in endometrial cancer risk-reduction strategy before genetic testing: 26/40 (65%). At 1-y follow-up, 16/16 (100%) MMR variant carriers were adherent to guidelines for risk-reduction, 9 (56%) of whom had had a prophylactic hysterectomy. By 3 y, 11/16 (69%) MMR variant carriers had a prophylactic hysterectomy. Among women with negative or uninformative genetic test results, none had a prophylactic hysterectomy after testing. |
Kwon et al (2011) developed a Markov Monte Carlo simulation model to compare 6 strategies for Lynch syndrome testing in women with endometrial cancer. Overall, the results suggested that IHC triage of women at any age who have at least 1 first-degree relative with a Lynch-associated cancer was the most cost-effective strategy (incremental cost-effectiveness ratio, $9126) for identifying Lynch syndrome and subsequent CRC cases. The model used published prevalence estimates of Lynch syndrome in all endometrial cancer patients of 2% (range, 1%-3%), and of 17% (range, 15%-20%) in endometrial cancer patients with at least 1 first-degree relative with a Lynch-associated cancer. Results are presented in Table 4.

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

<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 encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. As noted, in a 2006 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 (2010), hysterectomy improved survival among female colon cancer survivors with Lynch syndrome. This study also estimated that, for every 100 women diagnosed with Lynch syndrome-associated CRC, about 23 will be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Data on variant-specific risks have suggested that prophylactic gynecologic surgery benefits for carriers of MSH6 variants may offer less obvious benefits compared with harms, because the lifetime risk of endometrial cancer is lower than for carriers of MLH1 or MSH2 variants, and the lifetime risk of ovarian cancer is similar to the risk for the general population.

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

Direct evidence of clinical utility for genetic testing for Lynch syndrome is not available. Multiple studies have demonstrated clinical utility in testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and 1 cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed and did not follow recommended colonic surveillance. A positive genetic test for an MMR gene variant can also lead to changes in the management of other Lynch syndrome malignancies.

SUMMARY OF EVIDENCE

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

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, or (2) have colon cancer, or (3) have endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, or (4) are at-risk relatives of patients with Lynch syndrome, or (5) are without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria who receive genetic testing for MMR genes, the evidence includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in CRC. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known variant in an MMR gene, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who did and did not follow recommended colonic surveillance. A positive genetic test for an MMR variant can also lead to changes in the management of other Lynch syndrome malignancies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have CRC in whom MLH1 protein is not expressed on immunohistochemical analysis who receive genetic testing for \textit{BRAF V600E} or \textit{MLH1} promoter methylation, the evidence includes a few case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between \textit{BRAF V600E} variant and \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 that the technology results in a meaningful improvement in the net health outcome.

\textbf{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 from 3 physician specialty societies and 3 academic medical centers while this policy was under review in 2009. In general, those providing input were in agreement with the overall approach described in this policy.

\textbf{PRACTICE GUIDELINES AND POSITION STATEMENTS}

\textbf{National Comprehensive Cancer Network}

National Comprehensive Cancer Network (NCCN) guidelines (v.1.2017) for genetic/familial high-risk assessment of colorectal cancer (CRC)\textsuperscript{77} recommend 2 approaches to Lynch syndrome variant screening: (1) all newly diagnosed CRC or (2) all CRC patients diagnosed before age 70 plus those diagnosed at ages 70 and older who meet Bethesda guidelines. Additionally, NCCN guidelines (v.3.1017) recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years. Genetic testing is recommended for at-risk family members of patients with positive variants in \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, or \textit{PMS2}.\textsuperscript{78} NCCN 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 immunohistochemical (IHC) analysis to exclude a diagnosis of Lynch syndrome. These guidelines also address familial adenomatous polyposis (FAP; classical and attenuated), and \textit{MUTYH}-associated polyposis (MAP), consistent with the information in this evidence review.

Evaluation of Genomic Applications in Practice and Prevention recommendations noted that the current evidence is insufficient to clearly support benefit from genetic testing to the index patient with CRC if found to have Lynch syndrome. However, professional societies have reviewed the evidence and concluded that genetic testing likely has direct benefits for at least some patients with CRC and Lynch syndrome by differing recommendations for postsurgical surveillance, and for those who choose prophylactic surgical treatment instead of surveillance. NCCN guidelines for
colon cancer (v.2.2017)\textsuperscript{79} and for CRC screening (v.1.2017)\textsuperscript{80} recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year postsurgery and, if normal, again in 3 years, then every 5 years based on findings. However, because of the high likelihood of cancer, colonoscopy is recommended every 1 to 2 years throughout life for patients with Lynch syndrome before cancer diagnosis; and the high likelihood of a second primary cancer is based on a first cancer diagnosis.\textsuperscript{66} NCCN guidelines on genetic/familial high-risk assessment for colorectal indicate for \textit{MLH1}, \textit{MSH2}, and \textit{EPCAM} variant carriers that surveillance with colonoscopy should begin “at age 20 to 25 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years.”\textsuperscript{77} “\textit{MSH6} variant carriers should begin surveillance with colonoscopy at age 30 to 35 years, and \textit{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 \textit{MSH6} and \textit{PMS2} variant carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years.” “If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered.”

NCCN guidelines for colon cancer recommend that patients 70 years or younger plus those older than 70 years of age who meet the Bethesda guidelines be tested for the mismatch repair (MMR) protein for possible Lynch syndrome.\textsuperscript{79} These guidelines also indicate all colon cancer patients should be questioned about family history and considered for risk assessment as per NCCN colorectal screening guidelines. NCCN guidelines for uterine neoplasm also recommend universal screening for MMR genes.\textsuperscript{78}

\textbf{American College of Gastroenterology}

The American College of Gastroenterology issued practice guidelines (2015) for the management of patients with hereditary gastrointestinal cancer syndromes.\textsuperscript{81}

\textbf{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 \textit{MLH1}/\textit{MSH2}/\textit{MSH6}/\textit{PMS2} proteins and/or testing for microsatellite instability; tumors that demonstrate loss of \textit{MLH1} should undergo \textit{BRAF} testing or analysis for \textit{MLH1} promoter hypermethylation.
- “Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated \textit{BRAF} variant or hypermethylation of \textit{MLH1}), a known family variant associated with LS, or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.\textsuperscript{82}
- “Genetic testing of patients with suspected LS should include germline variant genetic testing for the \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, and/or \textit{EPCAM} genes or the altered gene(s) indicated by IHC testing.”

\textbf{Adenomatous polyposis syndromes}

“Familial adenomatous polyposis (FAP)/\textit{MUTYH}-associated polyposis/attenuated polyposis

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

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

American Society of Clinical Oncology and Society of Surgical Oncology

In 2015, the American Society of Clinical Oncology concluded that the European Society for Medical Oncology clinical practice guideline published in 2013 were based on the most relevant scientific evidence and therefore endorsed them with minor qualifying statements (in bold italics).83 The recommendations as relate to genetic testing hereditary CRC syndromes are summarized below:

- “Tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines.

- If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.

- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (eg, MSH2, MSH6, EPCAM, PMS2, or MLH1).

- Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis...

- Patients with multiple colorectal adenomas should be considered for full germline genetic testing of APC and/or MUTYH.”

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. 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>
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<td></td>
</tr>
<tr>
<td>NCT01447199</td>
<td>The Molecular Predisposition to Hereditary Nonpolyposis Colon Cancer (HNPPC)</td>
<td>2000</td>
<td>Sep 2017</td>
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<tr>
<td>NCT01850654</td>
<td>Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome</td>
<td>4000</td>
<td>Sep 2017</td>
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</table>
## 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>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>NCT01646112</td>
<td>Living in Lynch Syndrome Limbo: Exploring the Meaning of Uncertain Genetic Test Results</td>
<td>34</td>
<td>Feb 2016 (completed)</td>
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</tbody>
</table>

NCT: national clinical trial.

**CPT/HCPCS**

- **81201**: APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
- **81202**: APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
- **81203**: APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
- **81210**: BRAF (rB-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
- **81288**: MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
- **81292**: MLH1(mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- **81293**: MLH1(mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- **81294**: MLH1(mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication; deletion variants
- **81295**: MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- **81296**: MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- **81297**: MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication / deletion variants
- **81298**: MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- **81299**: MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- **81300**: MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication / deletion variants


*Contains Public Information*
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

PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic variant disorder/triplet repeat)

Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, variant scanning or duplication/deletion variants of 2-5 exons)

Immunochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)

Immunochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

Immunochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure

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-10 Diagnoses

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>
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<th>Notes</th>
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<tr>
<td>05-13-2011</td>
<td>Policy added to the bcbsks.com web site.</td>
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<tr>
<td>01-01-2012</td>
<td>In the Coding section:</td>
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<td>- Added the new codes: 81210, 81292-81301</td>
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<td>Changes</td>
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<td>- Replaced Diagnosis code 183.1 with correct code 183.2.</td>
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<td>- Removed HCPCS codes: S3828, S3829, S3830, S3831 (Deleted codes, effective April 1, 2012.)</td>
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<td>- Added CPT codes: 81401, 81406</td>
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<td>- Added new CPT codes: 81201, 81202, 81203 (Effective 01-01-2013)</td>
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<td>- Removed CPT codes: 83890, 83892, 83898, 83902, 83904, 83905, 83906, 83912 (Effective 12-31-2012)</td>
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<td>Updated Description section.</td>
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</table>
|            | - 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.                                                                                                                 |
|            | 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:                                                                                                                        |


Contains Public Information
Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

- 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 tumors" and "or endometrial" to read, "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 variant analysis."
- In Coding section:
  - Added CPT codes: 88341, 88342, 88344.

12-08-2017

- Updated Description section.
- In Policy section:
  - Added new Item I B, "HNPCC genetic testing is considered experimental / investigational for all other indications."
  - Previous Item I B is now Item I C.
  - Added new Item I D, "MSI testing or IHC analysis of tumors is considered experimental / investigational for all other indications."
  - Added new Item II B, "APC genetic testing is considered experimental / investigational for all other indications."
  - Previous Item II B is now Item II C.
  - Added new Item II D, "MAP genetic testing is considered experimental / investigational for all other indications."
- Updated Rationale section.
- In Coding section:
  - Removed ICD-9 codes.
- Updated References section.

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>
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<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
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<tr>
<td>1a. Diagnostic</td>
<td>X</td>
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<tr>
<td>1b. Prognostic</td>
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<tr>
<td>1c. Therapeutic</td>
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<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
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<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>
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<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td>X</td>
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<tr>
<td>5. Reproductive testing</td>
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<td>5a. Carrier testing: preconception</td>
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<tr>
<td>5b. Carrier testing: prenatal</td>
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<td>5c. In utero testing: aneuploidy</td>
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<td>5e. In utero testing: other</td>
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<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
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