Medical Policy

BlueCross BlueShield of Kansas
An Independent Licensee of the Blue Cross and Blue Shield Association

Title: Genetic Testing for Inherited Susceptibility to Colon Cancer, Including Microsatellite Instability Testing

Professional
Original Effective Date: May 13, 2011
Revision Date(s): January 1, 2012;
April 10, 2012; January 15, 2013;
March 26, 2013; August 21, 2013
Current Effective Date: March 26, 2013

Institutional
Original Effective Date: June 13, 2011
Revision Date(s): January 1, 2012;
April 10, 2012; January 15, 2013;
March 26, 2013; August 21, 2013
Current Effective Date: March 26, 2013

DESCRIPTION

Genetic testing is available for both affected individuals, as well as those at risk, for various type of hereditary cancer. This policy describes genetic testing r familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as HNPCC), MYH-associated polyposis, and Lynch syndrome-related endometrial cancer.

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

Familial adenomatous polyposis and associated variants

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.

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. (1) 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. (2) Thus, inheritance for high-risk colorectal cancer predisposition is autosomal recessive in contrast to FAP. When relatively few (i.e., between 10 and 99) adenomas are present and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include APC, MUTYH if APC is negative for mutations, and screening for mutations associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome. (3)

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 vs. MUTYH-associated polyposis vs. Lynch syndrome. These patients do not meet the clinical diagnostic criteria for classical FAP and have few adenomatous colonic polyps.
- Patients with colon cancer with a clinical picture or family history consistent with classical FAP.

Lynch syndrome

Patients with Lynch syndrome have a predisposition to 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. (4) 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. (3, 4) Estimated cumulative risks of any associated cancer for a carrier of a mutation in any MMR gene do not begin to increase until after age 30 years.

Lynch syndrome mutations are heterozygous; that is, only one of the 2 gene alleles contains a mutation. In rare cases both alleles contain the mutation, i.e., biallelic MMR gene mutations. This unusual syndrome has been described in multiple families and is to a large extent the result of consanguinity. (5) 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 (5)). 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. (6) 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. (7, 8)

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. (9) 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. (10)

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," i.e., methylation of promoter regions that control the expression of the MMR genes. (11-13) 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. Epimutations as a cause of Lynch syndrome are described only for informational purposes; no policy statement is made regarding this testing.

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.

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 note 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 when feasible may be considered **medically necessary** as an initial test in persons with colorectal cancer who meet the revised Bethesda criteria (see note below) in order to identify those persons who should proceed with HNPCC mutation analysis.

Note:
<u>Amsterdam II criteria:</u>

At least **three** relatives must have an HNPCC-related cancer ⅄(see below), and **all** of the following criteria must be present:

1. One must be a first-degree* relative of the other two; and
2. At least two successive generations must be affected; and
3. At least one of the relatives with cancer associated with HNPCC should be diagnosed before age 50 years; and
4. FAP (Familial Adenomatous Polyposis)should be excluded in the colorectal cancer cases (if any); and
5. Tumors should be verified whenever possible, from history and physical.
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.

<u>Revised Bethesda Criteria:</u>

One or more of the following criteria:

1. Colorectal cancer diagnosed before age 50 years; or
2. Synchronous or metachronous HNPCC-related cancers⅄(see below), regardless of age; or
3. Colorectal cancer with microsatellite instability-high (MSI-H) histology, where cancer is diagnosed before age 60 years; or
4. Colorectal cancer with one or more first-degree* relatives with an HNPCC-related cancer⅄(see below), with one of the cancers diagnosed under age 50 years; or
5. Colorectal cancer with two or more first*- or second-degree** relatives with an HNPCC-related cancer ⅄(see below), regardless of age.

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)

* 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.

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.

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

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.

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. (See Benefit Application section)
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 orIHC 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.

RATIONALE

FAP Genetic Testing

The policy for FAP genetic testing was based on a 1998 TEC Assessment, (16) which offered the following conclusions:

- Genetic testing for familial adenomatous polyposis (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 mutation.
- The optimal testing strategy is to define the specific genetic mutation in an affected family member and then test the unaffected family members to see if they have inherited the same mutation.

The additional policy information on attenuated FAP and on MYH-associated polyposis diagnostic criteria and genetic testing is based on information from GeneReviews (17) and from several publications (18-21) that build on prior, cited research. In addition, GeneReviews(17) summarizes clinical FAP genotype-phenotype correlations that could be used to determine different patient management strategies. The authors of the review conclude, however, that there is not yet agreement about using such correlations to direct management choices.

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

Lynch Syndrome and Colorectal Cancer Genetic Testing

The policy for Lynch syndrome genetic testing in colorectal cancer patients is based on an evidence report published by the Agency for Healthcare Research and Quality (AHRQ) (22), a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, (9) and an EGAPP recommendation for genetic testing in colorectal cancer. (23) 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 colorectal cancer:

- 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 (i.e., 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:
        - While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In one retrospective study, women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer
        - In one study, surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown. (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.

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 colorectal cancer for MMR gene mutations.

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 non-functional) and with the presence of MSH2 promoter hypermethylation, and, most importantly, have shown the co-segregation of these EPCAM mutations with Lynch-like disease in families. (13, 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 20-40% of patients/families who meet Lynch syndrome criteria, do not have a MMR mutation, but have MSI-high tumor tissue. Kempers et al. reported that carriers of an EPCAM deletion had a 75% (95% confidence interval [CI], 65–85) cumulative risk of colorectal cancer by age 70 years, not significantly different from that of carriers of an MSH2 deletion (77% (64–90); mean age at diagnosis was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0–27) by age 70, compared to carriers of a mutation in MSH2 (51% [95% CI, 33–69], p=0.0006). (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' 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 were deceased from Lynch-associated tumors and 5 were obligate carriers. In summary, the risk to develop colorectal cancer was high 93.1% (N=27/29) in deletion carriers over 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 cost-effectiveness may depend upon local factors.

Previous recommendations have used family history as an initial screen to determine who should proceed further to MMR laboratory testing. Recent studies have shown that limiting laboratory testing to patients who met even the more sensitive Revised Bethesda criteria (i.e., compared to the Amsterdam II criteria) would miss as much as 28% of Lynch syndrome cases. (32, 33) Family history is important for counseling families, but based on this and similar evidence, is not recommended as an initial screening tool to make decisions about testing patients who already have colorectal cancer. 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 (e.g., test only patients younger than age 50 years) is also not recommended. For example, Hampel et al. found that among 18 Lynch syndrome patients discovered among 500 unselected colorectal cancer patients, only 8 (44%) patients were diagnosed at age younger than 50 years. (32) 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. (33) Another group screened colorectal cancer patients who were younger than age 60 and identified 98 likely (MSI positive, BRAF negative) Lynch syndrome cases; of these, 47% were between ages 50 and 60. (34) A large study of Lynch syndrome family studies found that the cumulative risk of colorectal cancer in MMR mutation carriers was only 13% (95% CI, 9-19) by age 50, but 35% (95% CI, 25-49%) by age 70. (4) For MSH6 mutation carriers, however, colorectal cancer risks do not appear to increase until after age 60.

The estimated risk of stomach cancer in a large study of Lynch syndrome families was 6% (95% CI, 0.2-17%) for carriers of MLH1 mutations and warrants further study to address the utility of gastric surveillance. (4)

As the EGAPP recommendations noted, the evidence to date is limited to clearly support benefit from genetic testing to the index patient with colorectal cancer 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 colorectal cancer and Lynch syndrome on the basis of differing recommendations for post-surgical surveillance, and for those who choose prophylactic surgical treatment instead of surveillance. This policy is based on the evidence and professional society recommendations reviewed below.

In the absence of preventive surgery, heightened surveillance is recommended. The National Comprehensive Cancer Network (NCCN) guidelines for colon cancer (35) and for colorectal cancer screening (36) recommend post-surgical colonoscopy at 1 year and, if normal, again in 2-3 years, then every 3-5 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 prior to a cancer diagnosis, and on the high likelihood of a second primary cancer in those diagnosed with Lynch syndrome based on a first cancer diagnosis. (37) If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered. (36)

Early documentation of the natural history of colorectal cancer in highly selected families with a strong history of hereditary colorectal cancer indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, (38) in patients who already had colorectal cancer. As a result, in 1996, the Cancer Genetic Studies Consortium, a temporary NIH-appointed body, recommended that if colorectal cancer 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. (39) Although the average risk of a second primary is now estimated to be somewhat lower overall (see Description) in patients with Lynch syndrome and colorectal cancer, 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. (40) A mathematical model comparing total colectomy and IRA to hemicolectomy resulted in increased life expectancies of 2.3, 1, and 0.3 years for ages 27, 47, and 67, respectively; for Duke's A, life expectancies for the same ages are 3.4, 1.5, and 0.4, respectively. (41) 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 colorectal cancer, especially those who are younger. (42) 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

Recently, several groups have recommended screening endometrial cancer patients for Lynch syndrome. At the 2010 Jerusalem Workshop on Lynch Syndrome (43) it was proposed that all incident case of endometrial cancer be screened for Lynch syndrome using MMR-IH; Clarke and Cooper (44) note that Sloan Kettering Cancer Center screens all patients less than 50 years of age with endometrial cancer using MMR-IHC; as well as patients older than 50 with suggestive tumor morphology, lower uterine segment (LUS) location, personal/family history, or synchronous cell carcinoma of the ovary. Kwon et al. (45) recommended MMR-IHC screening of women with endometrial cancer at any age with at least one first-degree relative with a Lynch syndrome associated cancer.

The risk of endometrial cancer in MMR mutation carriers has been estimated at 34% (95% CI, 17-60%) by age 70, and of ovarian cancer 8% (95% CI, 2-39%) by age 70. (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 were analyzed for MSI, by IHC for expression of 4 MMR proteins, MMR gene methylation status and BRAF-mutations. Results are presented in Table 1 below; 92% of patients were more than 50 years of age. (46)

Table 1. Testing unselected endometrial cancer patients for Lynch syndrome.

Result	**N**	**% (95% CI)**
Stable MMS and normal protein staining	137	76%
MSI-H and MLH1 absent	32	
--Sporadic MSI-H	31	17% (13-24%)
Likely to have Lynch syndrome	11	6% (3-11%)
--mutation positive	7	
--no mutation found	3	
--refuses further DNA testing	1	

Another study examined 625 endometrial cancer patients who underwent hysterectomy; endometrial cancer was classified as LUS in 9 patients. (47) Twenty-seven randomly chosen patients from the non-LUS group were compared to the LUS group and no statistically significant differences were found between groups with regard to MSI status or IHC findings. The incidence of Lynch syndrome in the LUS group was 1 in 9. (48, 49)

Kwon (45) developed a Markov Monte Carlo simulation model to compare six 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 (FDR) with a Lynch-associated cancer, was the most cost effective strategy (ICER = $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 one FDR with a Lynch-associated cancer. Results are presented in Table 2:

Table 2. Modeling of endometrial cancer patient screening strategies for detecting Lynch syndrome

Testing Strategy	No. cases subject to IHC triage	No. identified with Lynch syndrome	No. subsequent CRC cases
Amsterdam II criteria	NA	539	2582
Age <50, and at least 1 FDR (Lynch-associated cancer)	NA	530	2470
IHC triage < age 50	6285	520	2442
IHC triage < age 60	16226	548	2450
IHC triage at any age at least 1 FDR with Lynch-associated cancer	**5786**	**755**	**2442**
IHC triage all endometrial cancers	45000	827	2413

Female patients with Lynch syndrome who choose risk-reducing surgery are also encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. As already noted, in one retrospective study, women who chose this option had no gynecologic cancer over 10 years whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer. (50) In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome. (51) This study also estimated that for every 100 women diagnosed with Lynch syndrome-associated colorectal cancer, about 23 will be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Recent data on mutation-specific risks suggests that prophylactic gynecological surgery benefits for carriers of MSH6 mutations may offer less obvious benefits compared to harms as lifetime risk of endometrial cancer is lower than for carriers of MLH1 or MSH2 mutations, and lifetime risk of ovarian cancer is similar to the risk for the general population. (4)

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. (29, 30, 52) Women with EPCAM deletions consequently have a life-time risk of developing endometrial cancer decreased by 10-fold when compared to MMR gene mutation carriers. This might support a clinical management scenario rather than prophylactic surgery. (30) An alternative to prophylactic surgery is surveillance for endometrial cancer using transvaginal ultrasound (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. (53) Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated successful at improving survival. (53)

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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. 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 general, those providing input were in agreement with the overall approach described in this policy.

Summary

Results of testing for the APC mutation in individuals with a family history of FAP, or a known APC mutation in the family, lead to changes in surveillance and prophylactic treatment. For patients with a positive result, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. Therefore APC testing is medically necessary for patients with a family history of FAP or a known APC mutation in the family. A related familial polyposis syndrome, MUTYH-associated polyposis (MAP) syndrome, is associated with mutations in the MUTYH gene. Testing for this genetic mutation is medically necessary when the differential diagnosis includes both FAP and MAP, since 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.

A substantial portion of patients with colorectal cancer will be found to have Lynch syndrome, which is associated with mutations in the MMR gene. A positive genetic test for the MMR mutation can lead to enhanced surveillance, changes in recommendations about treatment options, and possible prophylactic treatment for other Lynch syndrome malignancies. Therefore, testing for Lynch syndrome in patients with newly diagnosed colorectal cancer and in patients at high risk for Lynch syndrome, defined by meeting the clinical criteria such as Amsterdam II or Revised Bethesda, is considered medically necessary.

Women with endometrial cancer are also at risk for Lynch syndrome, at a low prevalence; the prevalence is increased substantially when the population is limited to those (at any age) with a first-degree relative diagnosed with a Lynch-associated cancer. Those found to have a MMR mutation will also benefit from enhanced colorectal cancer surveillance and prophylactic treatments. Therefore, testing for Lynch syndrome in patients with newly diagnosed endometrial cancer who also have a first degree relative diagnosed with a Lynch-associated cancer may be considered medically necessary. The EPCAM mutation is less common than MMR mutations as a cause of Lynch syndrome, and should be part of the diagnostic testing for Lynch syndrome in patients who are negative for all MMR mutations but who screen positive for microsatellite instability and lack MSH2 immunohistochemistry evidence of protein expression.

Practice Guidelines and Position Statements

The European Society for Medical Oncology (ESMO) published clinical practice guidelines for familial colorectal cancer risk in 2010. (2) These guidelines addressed Lynch Syndrome, familial adenomatous polyposis, and MUTYH-associated polyposis. No specific recommendations were made regarding how to initially identify Lynch syndrome cases; several methods, including clinical criteria and universal screening of all CRC cases, were mentioned. Other ESMO recommendations are consistent with the information in this policy.

The National Comprehensive Cancer Network (NCCN) guideline for colorectal cancer screening notes that screening of all colorectal and endometrial cancers for Lynch syndrome mutations has been implemented at some centers and does not recommend for or against this practice. (36) The guideline does not specifically mention EPCAM deletion testing but does indicate that individuals with loss of MSH2 and/or MSH6 protein expression by immunohistochemistry, regardless of germline MMR mutation status, should be followed as though they have Lynch syndrome. These guidelines also address familial adenomatous polyposis (classical and attenuated), and MUTYH-associated polyposis, consistent with the information in this policy.

The American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) recommends offering prophylactic total abdominal hysterectomy to female patients with colorectal cancer 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. (42)

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.

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
81292	MLH1(mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non0polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1(mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non0polyposis 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 analysiso
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
81301	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
81401	Molecular pathology procedure, Level 2 (eg. 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using non sequencing target analysis], or detection of a dynamic mutation disorder / triplet repeat); MUTYH (mutY homolog[E. coli]) (eg, MYH-associated polyposis), common variants (eg, Y165C, G382D)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication / deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia); MUTYH (mutY homolog [E. coli] (eg, MYH-associated polyposis", full gene sequence

- There are CPT genetic testing modifiers specific to MLH1 (-0J), and MSH2, MSH6 or PMS2 (-0K).

- There are no specific CPT codes for genetic testing; testing is typically coded for using a series of CPT codes describing the individual steps in the testing process (some codes may be used more than once in the series of codes for a genetic test). The CPT codes are similar to the codes used for other types of genetic testing, i.e., genetic testing for breast cancer, and are listed below. The exact methodology used will depend on the clinical situation. For example, genetic testing for a single known mutation involves fewer steps than the testing required to identify one of many possible mutations.

Note: The series of 4 HCPCS codes (above) specifically describe genetic sequencing for MLH1 and MSH2, individually or together, or genetic testing for a single mutation in a known affected family. Therefore, these codes could be used in lieu of using CPT coding for the individual components of genetic testing.

DIAGNOSIS

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 Diagnosis *(Effective October 1, 2014)*

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

05-13-2011	Policy added to the bcbsks.com web site.
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)*

REFERENCES

1. Vogt S, Jones N, Christian D et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology 2009; 137(6):1976-85 e1-10.
2. Balmana J, Castells A, Cervantes A. Familial colorectal cancer risk: ESMO Clinical Practice Guidelines. Ann Oncol 2010; 21 Suppl 5:v78-81.
3. Gala M, Chung DC. Hereditary colon cancer syndromes. Semin Oncol 2011; 38(4):490-9.
4. Bonadona V, Bonaiti B, Olschwang S et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011; 305(22):2304-10.
5. Durno CA, Holter S, Sherman PM et al. The gastrointestinal phenotype of germline biallelic mismatch repair gene mutations. Am J Gastroenterol 2010; 105(11):2449-56.
6. Umar A, Boland CR, Terdiman JP et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004; 96(4):261-8.
7. Wu Y, Berends MJ, Mensink RG et al. Association of hereditary nonpolyposis colorectal cancer-related tumors displaying low microsatellite instability with MSH6 germline mutations. Am J Hum Genet 1999; 65(5):1291-8.
8. Goel A, Nagasaka T, Spiegel J et al. Low frequency of Lynch syndrome among young patients with non-familial colorectal cancer. Clin Gastroenterol Hepatol 2010; 8(11):966-71.
9. Palomaki GE, McClain MR, Melillo S et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 2009; 11(1):42-65.
10. Bouzourene H, Hutter P, Losi L et al. Selection of patients with germline MLH1 mutated Lynch syndrome by determination of MLH1 methylation and BRAF mutation. Fam Cancer 2010; 9(2):167-72.
11. Hesson LB, Hitchins MP, Ward RL. Epimutations and cancer predisposition: importance and mechanisms. Curr Opin Genet Dev 2010; 20(3):290-8.
12. Hitchins MP. Inheritance of epigenetic aberrations (constitutional epimutations) in cancer susceptibility. Adv Genet 2010; 70:201-43.
13. Niessen RC, Hofstra RM, Westers H et al. Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. Genes Chromosomes Cancer 2009; 48(8):737-44.

14. Vasen HF, Watson P, Mecklin JP et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999; 116(6):1453-6.
15. Lipton LR, Johnson V, Cummings C et al. Refining the Amsterdam Criteria and Bethesda Guidelines: testing algorithms for the prediction of mismatch repair mutation status in the familial cancer clinic. J Clin Oncol 2004; 22(24):4934-43.
16. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Genetic testing for inherited susceptibility to colorectal cancer: part I – adenomatous polyposis coli gene mutations. TEC Assessments 1998, Volume 13, Tab 10.
17. Burt RW, Jasperson KW. APC-associated polyposis conditions. 2008. Available online at: http://www.ncbi.nlm.nih.gov/bookshelf/bf.fcgi?book=gene&part=fap. Last accessed June 2009.
18. Kastrinos F, Syngal S. Recently identified colon cancer predispositions: MYH and MSH6 mutations. Semin Oncol 2007; 34(5):418-24.
19. Lefevre JH, Parc Y, Svrcek M et al. APC, MYH, and the correlation genotype-phenotype in colorectal polyposis. Ann Surg Oncol 2009; 16(4):871-7.
20. Avezzu A, Agostini M, Pucciarelli S et al. The role of MYH gene in genetic predisposition to colorectal cancer: another piece of the puzzle. Cancer Lett 2008; 268(2):308-13.
21. Balaguer F, Castellvi-Bel S, Castells A et al. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case-control, population-based study. Clin Gastroenterol Hepatol 2007; 5(3):379-87.
22. Bonis P, Trikalinos T, Chung M. Hereditary Nonpolyposis Colorectal Cancer: Diagnostic Strategies and Their Implications. Evidence Report/Technology Assessment No. 150 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). 2007;AHRQ Publication No. 07-E008.(May). Available online at
23. http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1b.chapter.80582.
24. Group EoGAiPaPEW. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009; 11(1):35-41.
25. Kloor M, Voigt AY, Schackert HK et al. Analysis of EPCAM protein expression in diagnostics of Lynch syndrome. J Clin Oncol 2011; 29(2):223-7.
26. Kuiper RP, Vissers LE, Venkatachalam R et al. Recurrence and variability of germline EPCAM deletions in Lynch syndrome. Hum Mutat 2011; 32(4):407-14.
27. Kovacs ME, Papp J, Szentirmay Z et al. Deletions removing the last exon of TACSTD1 constitute a distinct class of mutations predisposing to Lynch syndrome. Hum Mutat 2009; 30(2):197-203.
28. Ligtenberg MJ, Kuiper RP, Chan TL et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet 2009; 41(1):112-7.

29. Rumilla K, Schowalter KV, Lindor NM et al. Frequency of deletions of EPCAM (TACSTD1) in MSH2-associated lynch syndrome cases. J Mol Diagn 2011; 13(1):93-9.
30. Kempers MJ, Kuiper RP, Ockeloen CW et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol 2011; 12(1):49-55.
31. Grandval P, Baert-Desurmont S, Bonnet F et al. Colon-specific phenotype in Lynch syndrome associated with EPCAM deletion. Clin Genet 2012; 82(1):97-9.
32. Overbeek LI, Ligtenberg MJ, Willems RW et al. Interpretation of immunohistochemistry for mismatch repair proteins is only reliable in a specialized setting. Am J Surg Pathol 2008; 32(8):1246-51.
33. Hampel H, Frankel WL, Martin E et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008; 26(35):5783-8.
34. Canard G, Lefevre JH, Colas C et al. Screening for Lynch syndrome in colorectal cancer: are we doing enough? Ann Surg Oncol 2012; 19(3):809-16..
35. Schofield L, Watson N, Grieu F et al. Population-based detection of Lynch syndrome in young colorectal cancer patients using microsatellite instability as the initial test. Int J Cancer 2009; 124(5):1097-102.
36. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology, Colon Cancer, v I.2012. Available at http://www.nccn.org 2011.
37. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology, Colorectal Cancer Screening, v 2.2011. Available at http://www.nccn.org 2011.
38. de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G et al. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. Dis Colon Rectum 2002; 45(12):1588-94.
39. Fitzgibbons RJ, Jr., Lynch HT, Stanislav GV et al. Recognition and treatment of patients with hereditary nonpolyposis colon cancer (Lynch syndromes I and II). Ann Surg 1987; 206(3):289-95.
40. Burke W, Petersen G, Lynch P et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. JAMA 1997; 277(11):915-9.
41. Van Dalen R, Church J, McGannon E et al. Patterns of surgery in patients belonging to amsterdam-positive families. Dis Colon Rectum 2003; 46(5):617-20.
42. de Vos tot Nederveen Cappel WH, Buskens E, van Duijvendijk P et al. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. Gut 2003; 52(12):1752-5.
43. Guillem JG, Wood WC, Moley JF et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. J Clin Oncol 2006; 24(28):4642-60.
44. Boland CR, Shike M. Report from the Jerusalem workshop on Lynch syndrome-hereditary nonpolyposis colorectal cancer. Gastroenterology 2010; 138(7):2197 e1-7.

45. Clarke BA, Cooper K. Identifying Lynch syndrome in patients with endometrial carcinoma: shortcomings of morphologic and clinical schemas. Adv Anat Pathol 2012; 19(4):231-8.
46. Kwon JS, Scott JL, Gilks CB et al. Testing women with endometrial cancer to detect Lynch syndrome. J Clin Oncol 2011; 29(16):2247-52.
47. Leenen CH, van Lier MG, van Doorn HC et al. Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer </= 70 years. Gynecol Oncol 2012; 125(2):414-20.
48. Masuda K, Banno K, Hirasawa A et al. Relationship of lower uterine segment cancer with Lynch syndrome: A novel case with an hMLH1 germline mutation. Oncol Rep 2012; 28(5):1537-43.
49. Goodfellow PJ, Buttin BM, Herzog TJ et al. Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers. Proc Natl Acad Sci U S A 2003; 100(10):5908-13.
50. Hampel H, Frankel W, Panescu J et al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res. 2006; 66(15):7810-7.
51. Schmeler KM, Lynch HT, Chen LM et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006; 354(3):261-9.
52. Obermair A, Youlden DR, Young JP et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer 2010; 127(11):2678-84.
53. Lynch HT, Riegert-Johnson DL, Snyder C et al. Lynch syndrome-associated extracolonic tumors are rare in two extended families with the same EPCAM deletion. Am J Gastroentero. 2011; 106(10):1829-36.
54. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand 2011; 90(5):437-44.

Other References:

1. Blue Cross and Blue Shield of Kansas Surgery Liaison, August 2010; August 2011.