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Medical Policy Manual

Topic: Genetic Testing for Inherited Susceptibility to Colon Cancer

Date of Origin: January 2012

Section: Genetic Testing

Last Reviewed Date: January 2014

Policy No: 06

Effective Date: March 1, 2014

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Currently, there are two well-defined types of hereditary conditions that predispose affected individuals to colorectal cancer (CRC): familial adenomatous polyposis (FAP) with associated variants (collectively referred to as APC-associated polyposis) and Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer, or HNPCC).

APC-Associated Polyposis

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

Familial Adenomatous Polyposis (FAP) (also known as Classical FAP)

FAP is characterized by the presence of hundreds to thousands of precancerous colon polyps, appearing on average at 16 years of age. If left untreated, all affected individuals eventually develop CRC. The mean age of CRC diagnosis in untreated individuals is 39 years.

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.

Gardner Syndrome

FAP 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). These collective extraintestinal manifestations of FAP are referred to as Gardner Syndrome.

Turcot Syndrome

When associated with central nervous system (CNS) tumors, FAP is referred to as Turcot syndrome.

Attenuated FAP (AFAP)

Like FAP, *A*FAP is characterized by a significant risk for CRC as well, but there are fewer precancerous colonic polyps (10-99, 30 on average). The average age of CRC diagnosis in AFAP patients is 50-55 years. The disorder is associated with fewer extraintestinal cancers than FAP but with a significantly higher risk compared to the general population. The lifetime risk of CRC in individuals with AFAP is about 70% by the age of 80.

AFAP is inherited in an autosomal dominant manner and explained by germline mutations in the APC gene as well. However, fewer than 30% of AFAP patients have APC mutations and may have mutations in the MUTYH gene instead (see below).

MUTYH-Associated Polyposis (MAP) (formerly MYH-associated polyposis)

MAP occurs with a similar frequency to FAP. While MAP also has clinical features similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. In contrast to FAP and AFAP, MAP is explained by mutations in the MUTYH gene and is inherited in an autosomal recessive manner. Biallelic MUTYH mutations are associated with a cumulative CRC risk of about 80% by age 70. Monoallelic MUTYH mutation-associated risk of CRC appears to be relatively minimal, although still under debate.

Lynch Syndrome

Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC) is a hereditary disorder characterized by a high predisposition to colon cancer (27-45% for men and 22-38% for women by age 70) and cancers of the endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain (usually glioblastomas), sebaceous gland adenomas and keratoacanthomas, and small intestine.[1,2] These cancers are sometimes collectively referred to as HNPCC- or Lynch syndrome-associated cancers. The syndrome is estimated to account for approximately 1-3% of all colorectal cancers.[3] Lynch syndrome is also 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.

Lynch Syndrome and Mutations In Mismatch Repair (MMR) Genes

Lynch syndrome is inherited in an autosomal dominant manner and may be caused by any of a large number of possible mutations in one of the several mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2, and rarely MLH3). Mutations in MMR genes prevent normal DNA repair in the repetitive DNA sequences called microsatellites. This results in microsatellite instability (MSI) and ultimately leads to an increased risk for malignancy.

A majority of Lynch syndrome patients have mutations in either MLH1 or MSH2, and testing for MMR gene mutations is often limited to these two genes. If results are negative, MSH6 and PMS2 genes may be tested for mutations next. Large gene sizes and the difficulty of detecting mutations in these genes make direct sequencing a time- and cost- consuming process. Therefore, additional indirect screening methods are needed to determine which patients should proceed to direct sequencing for MMR gene mutations. Available tumor screening methods include MSI testing and immunohistochemical (IHC) testing. BRAF V600E 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.

Lynch Syndrome and Mutations in Non-Mismatch Repair (non-MMR) Genes

Deletions in the non-MMR EPCAM (epithelial cell adhesion molecule) gene may result in inactivation of the non-mutated MSH2 gene, thereby causing Lynch syndrome. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and IHC shows a lack of MSH2 expression, but no MSH2 mutation is found by sequencing.

Amsterdam and Bethesda Criteria

- The objective of the Amsterdam I and revised Amsterdam II criteria is to define families that are very likely to have Lynch syndrome.[3] In another words, these criteria aim to "establish the diagnosis of Lynch syndrome based upon familial clustering of HNPCC-related tumors."[4] The revised Amsterdam II criteria are broader than Amsterdam I as they consider both colorectal *and* HNPCC-associated cancers in the assessment.[3] The Amsterdam criteria were originally developed by the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) in order to standardize family selection criteria for collaborative research on Lynch syndrome. Consequently, these criteria are not without limitations when applied to clinical diagnosis. In recent years, "family history is considered less useful as the first step in identifying Lynch syndrome in individuals *with* newly diagnosed colorectal cancer (CRC) than strategies involving the analysis of tumor samples (eg, MSI, IHC)."[5,6] However, family history is still considered "an important component of cancer risk assessment in the general population"[6]
- The Bethesda criteria were developed with a different purpose than the Amsterdam criteria.[1,7,8] They were designed to "help predict which patients *with* colorectal cancer are likely to have a mismatch-repair mutation and should thus undergo further testing."[4]

Regulatory Status

The majority of genetic tests are laboratory derived tests that are not subject to U.S. Food and Drug Administration (FDA) approval. Labs are subject to Clinical Laboratory Improvement Amendment (CLIA) regulations that monitor high-complexity testing. The GeneTests website lists the U.S.-located laboratories that offer this service.

Genetic Testing Panels

Sequencing of FAP, AFAP, MUTYH or Lynch syndrome mutations may be offered in combination with other gene or chromosomal microarray tests that are not associated with Lynch syndrome or FAP. Medical necessity must be established for each genetic test included in a panel. When FAP, AFAP, MUTYH or Lynch syndrome analysis is bundled with any other genetic test, additional Medical Policies may apply.

MEDICAL POLICY CRITERIA

I. Genetic testing for APC gene mutations may be considered **medically necessary** for one of the following:

A. At-risk relatives of patients with familial adenomatous polyposis (FAP) and/or a known APC mutation.

"At risk relatives" primarily refers to first-degree relatives e.g., mother, father, sister, brother, children of the patient.

B. Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome.

II. Genetic testing for MUTYH gene mutations may be considered **medically necessary** when both of the following criteria are met:

A. There is a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome; and

B. There is a negative result for APC gene mutations.

A family history of no parents or children with FAP is consistent with MUTYH-associated polyposis (autosomal recessive).

III. Genetic testing for MMR gene mutations (MLH1, MSH2, MSH6, PMS2) may be considered **medically necessary** when any one of the following criteria is met:

A. Lynch syndrome is suspected in patients *with* colorectal cancer.

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 (MSI *and* IHC) are not necessary.

B. Lynch syndrome is suspected in patients with endometrial cancer and one first-degree relative is diagnosed with a Lynch-associated cancer (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, or small bowel).

C. A known MMR mutation has been identified in a first-degree relative with Lynch syndrome.

D. There is a differential diagnosis of attenuated FAP vs. MUYH-associated polyposis vs. Lynch syndrome.

E. Lynch syndrome is suspected in patients *without* colorectal cancer (including both cancer-

free individuals and individuals with an HNPCC-associated cancer* other than CRC) but with a family history meeting the Amsterdam II or modified Amsterdam II criteria, when no affected family members have been tested for MMR mutations.

Amsterdam II criteria

The family (from one lineage), including the index patient, must meet *all* of the following criteria:

1. Three or more family members with a histologically-verified HNPCC-associated cancer*, one of whom is a first-degree relative of the other two; and
2. HNPCC-associated cancer* involving at least two successive generations; and
3. HNPCC-associated cancer* in one or more of the affected family members is diagnosed before 50 years of age; and
4. Familial adenomatous polyposis is excluded in any cases of colorectal cancer.

*HNPPC-associated cancers include cancers of the endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain (usually glioblastomas), sebaceous gland adenomas and keratoacanthomas, and small intestine.

Modified Amsterdam II Criteria

For very small families the modified Amsterdam II criteria may be applied. One of the following criteria must be met:

1. Two colorectal cancers in first-degree relatives involving at least two generations, with at least one individual diagnosed by age 55.
2. Two first-degree relatives affected by colorectal cancer and a presence of a third relative with an unusual early-onset neoplasm or endometrial cancer diagnosed at age 50 or less.

Note: Criterion IV.E. addresses testing of individuals *without* CRC; therefore the Revised Bethesda criteria do not apply. The Revised Bethesda criteria aid in predicting which patients *with* colorectal cancer are likely to have a mismatch-repair mutation and should undergo further testing.

IV. Genetic testing for EPCAM mutations may be considered **medically necessary** when any one of the following criteria (A-C) is met:

A. To diagnose Lynch syndrome in patients *with* colorectal cancer when either of the following criteria (1 or 2) is met:

1. Tumor tissue shows lack of MSH2 expression by immunohistochemistry and the patient is negative for a germline mutation in MSH2; *OR*

2. Tumor tissue shows a high level of microsatellite instability and the patient is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6*; OR*

B. At-risk relatives* of patients with Lynch syndrome with a known *EPCAM* mutation; *OR*

*At risk relatives primarily refers to first-degree relatives e.g., mother, father, sister, brother, children of the patient.

C. Patients *without* colorectal cancer but with a family history meeting the Amsterdam II or modified Amsterdam II criteria, when no affected family members have been tested for MMR mutations, and when sequencing for MMR mutations is negative.

For Amsterdam II and modified Amsterdam II criteria see IV.E. above.

V. Genetic testing for BRAF V600E or MLH1 promoter methylation may be considered **medically necessary** to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

VI. Pre- and post-test genetic counseling may be considered **medically necessary** as an adjunct to the genetic testing itself.

SCIENTIFIC EVIDENCE

FAP Genetic Testing

The policy for FAP genetic testing was based on a 1998 TEC Assessment[9] , 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[10] and from several publications[11-15] that build on prior, cited research. GeneReviews specifically notes that, “the presence of 100 or more colorectal polyps is not specific to FAP” and that, “genetic testing of APC may help distinguish FAP from MUTYH-associated polyposis (MAP) or colonic polyposis conditions of unknown etiology.” In addition, GeneReviews[10] 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.

Lynch Syndrome and Colorectal Cancer Genetic Testing

<u>MMR Genetic Testing</u>

Agency for Healthcare Research and Quality (AHRQ) / Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Evidence Assessment

The policy for Lynch syndrome genetic testing in colorectal cancer patients is based on an evidence report published by the AHRQ[16] , a supplemental assessment to that report contracted by the EGAPP Working Group[5] , and an EGAPP recommendation for genetic testing in colorectal cancer.[6] Based on the AHRQ report and supplemental assessment, the EGAPP report 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 and IHC screening tests for MMR mutations have similar sensitivity and specificity. MSI screening has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6, and a specificity of about 90% for all. It is likely that, using high quality MSI testing methods, these parameters can be improved. 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.
    - 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.
    - Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. About half of relatives received counseling, and 95% of these chose MMR gene mutation testing. Among those positive for MMR gene mutations, uptake of colonoscopic surveillance beginning at age 20–25 years was high at 53–100%.
        - One long-term, nonrandomized controlled study and one cohort study of Lynch syndrome family members found significant reductions in colorectal cancer among those who followed recommended colonic surveillance vs. those who did not.
        - Surveillance, prevention for other Lynch syndrome cancers (for detail, refer to last outline bullet)
    - The chain of evidence from descriptive studies and expert opinion (as noted below) is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., cancer index patient).
        - Subtotal colectomy is recommended as an alternative to segmental resection, but has not been shown superior in follow-up studies
        - Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.
        - Surveillance, prevention for other Lynch syndrome cancers:
            - While invasive and not 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.[17] 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 2012, further support for universal MMR gene mutation testing of colorectal cancer patients was reported by Moreira and colleagues in a comparison of universal testing of colorectal cancer patients to alternate screening approaches.[18] The alternate screening approaches included the use of the Bethesda guidelines, the Jerusalem recommendations and a selective strategy including only those diagnosed with colorectal cancer before age 70 or after age 70 if the Bethesda guidelines were met. In the analysis of 10,206 newly diagnosed colorectal cancer patients from 4 large cohort studies, the universal screening approach was found to be superior to the other screening approaches in the population-based cohorts (n=3671 probands). However, the diagnostic yield differences between the screening approaches were small and the false positive yield was 2.5% with universal screening. Whereas, in the selective strategy, 34.8% fewer patients required tumor MMR testing and 28.6% fewer analyses of MMR mutations resulting in 4.9% missed Lynch syndrome cases, suggesting this may be a reasonable compromise which could result in improved detection of MMR mutations.

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. 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.

American Society of Clinical Oncology (ASCO)/ Society of Surgical Oncology (SSO) Recommendations

As the EGAPP recommendations have noted, the evidence to date is limited in regards to benefits derived from patients with colorectal cancer who undergo testing and are 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 who choose prophylactic surgical treatment.

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%[19] 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.[20] Although the average risk of a second primary is now estimated to be somewhat lower overall 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.[21] 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.[22] Based on this work, the joint ASCO and 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.[23] 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.

EPCAM Testing

Several studies characterized EPCAM deletions and 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.[24-29] 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, 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).[30]

BRAF V600E Testing

BRAF mutation V 600E or MLH1 promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH1 protein expression by IHC testing for MLH1. The presence of BRAF V600E or absence of MLH1 protein expression rarely occurs in Lynch syndrome and would eliminate the need for further germline mutation analysis for a Lynch syndrome diagnosis.[31-33]

In 2013, Capper et al. reported on a technique of BRAF V600E-specific immunohistochemistry (VE1) IHC testing for BRAF-mutations on a series of 91 MSI-H CRC patients.[34] The authors detected BRAF-mutated CRC with 100% sensitivity and 98.8% specificity. VE1 positive lesions were detected in 21% of MLH1-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Although additional studies are needed to confirm the efficacy of this technique, VE1 IHC testing for BRAF may be an alternative to MLH1 promoter methylation analysis and a method for avoiding further MMR testing.

Lynch Syndrome and Endometrial Cancer Genetic Testing

The ASCO/SSO review discussed above also 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.[23] This recommendation is based on the high rate of endometrial cancer in mutation-positive individuals (30–64% in studies that may be biased by strong family history; overall, possibly as low as 20–25%[7]) and the lack of efficacy of screening. A recent study estimated the risk of endometrial cancer in mutation carriers at 34% by age 70 (95% CI, 17-60%), and of ovarian cancer at 8% by age 70 (95% CI, 2-39%).[35] Risks do not appear to appreciably increase until after age 40. When surgery is chosen, oophorectomy should also be performed because of the high incidence of ovarian cancer in Lynch syndrome (12%[21]). 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.[5] In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome.[36] 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.[35] An alternative to prophylactic surgery is surveillance for endometrial cancer using transvaginal ultrasound and endometrial biopsy. Evidence indicates that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet indicates surveillance reduces mortality due to endometrial cancer. Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.

Recently, several groups recommended screening endometrial cancer patients for Lynch syndrome. At the 2010 Jerusalem Workshop on Lynch Syndrome it was proposed that all incident cases of endometrial cancer be screened for Lynch syndrome using MMR-IH.[37] Clarke and Cooper noted 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.[38] Kwon et al. recommended MMR-IHC screening of women with endometrial cancer at any age with at least one first-degree relative with a Lynch syndrome associated cancer.[39]

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 preventive hysterectomy.[30,40,41] Women with *EPCAM* deletions consequently have a life-time risk of developing endometrial cancer decreased by 10-fold when compared with MMR gene mutation carriers. This might support a clinical management scenario rather than prophylactic surgery.[40]

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)[42]

The NCCN guideline for colorectal cancer screening recommend two approaches to Lynch syndrome mutation screening of either:

1. all colorectal cancers or
2. colorectal cancer patients diagnosed before age 70 and those ages 70 and older when meeting Bethesda guidelines.

Additionally, the colorectal cancer screening guidelines also recommend screening for Lynch syndrome for all endometrial cancer patients less than 50 years old. These guidelines note immunohistochemistry and sometimes microsatellite instability testing may be performed at some centers on all newly diagnosed colorectal and endometrial cancer patients to determine need for genetic testing for Lynch syndrome mutations regardless of family history. The NCCN guidelines on uterine neoplasms indicate all endometrial cancer patients, especially those younger than 55 years, should be considered for testing for genetic mutations such as Lynch syndrome.

The NCCN 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.

Genetic testing is recommended for at-risk family members of patients with positive mutations in MLH1, MSH2, MSH6 or PMS2. The NCCN guidelines also indicate BRAF V600E testing or MLH1 promoter methylation testing may be used when MLH1 is not expressed in the tumor on immunohistochemical (IHC) analysis to exclude a diagnosis of Lynch syndrome. As noted in the NCCN guidelines, “the presence of a BRAF mutation indicates MLH1 expression is downregulated by somatic methylation of the promoter region of the gene and not by germline mutation.”

The NCCN guidelines also address familial adenomatous polyposis (classical and attenuated), and MUTYH-associated polyposis and recommend genetic testing for patients with a personal history of > 10 adenomas in order to differentiate between APC and MUTYH mutations.

These NCCN guidelines are based on Level 2A evidence which is based upon lower-level evidence with uniform NCCN consensus that the intervention is appropriate.

Summary

<u>APC-Associated Polyposis</u>

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.

<u>Lynch Syndrome</u>

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 is considered medically necessary.

The identification of a BRAF V600E mutation would eliminate the need for further germline mutation analysis in patients with suspected Lynch syndrome. Therefore, in the absence of colorectal tumor MLH1 protein expression on immunohistochemistry (IHC) testing, additional IHC testing for BRAF V600E or MLH1 promoter methylation may be 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.

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Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12

KRAS and BRAF Mutation Analysis in Metastatic Colorectal Cancer, Genetic Testing, Policy No. 13

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy, Genetic Testing, Policy No. 41

Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64

CODES	NUMBER	DESCRIPTION
CPT	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 *(v-raf murine sarcoma viral oncogene homolog B1)* (eg, colon cancer), gene analysis, V600E variant.
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	; known familial variants
	81294	; 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	; known familial variants
	81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary duplication/deletion variants duplication/deletion variants
	81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis

CODES	NUMBER	DESCRIPTION
		colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	; known familial variants
	81300	; 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
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	; known familial variants
	81319	; duplication/deletion variants
	88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)
HCPCS	None	
	~~S3833~~	~~Complete APC gene sequence analysis for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP~~ (Deleted 01/01/2014)
	~~S3834~~	~~Single mutation analysis (in individual with a known APC mutation in the family) for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP~~ (Deleted 01/01/2014)