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 MUTYH-associated polyposis (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, AFAP 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 the risk is 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, PSM1, and EXO1). 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 (70%) 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. 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. Therefore, *BRAF*-positive samples need not be further tested by MLH1 sequencing.

**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.”[5] 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 (e.g., MSI, IHC).”[6,7] However, family history is still considered “an important component of cancer risk assessment in the general population.”[7]

The Bethesda criteria were developed with a different purpose than the Amsterdam criteria.[1,8,9] 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.”[5]
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, MUTYH, mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) and/or EPCAM gene mutations may be considered medically necessary when any one of the following criteria (A-E) is met:

   A. At-risk relatives (see Policy Guidelines) of patients with either of the following:
      1. Familial adenomatous polyposis (FAP); or
      2. A known APC, MUTYH, MLH1, MSH2, MSH6, PMS2 and/or EPCAM mutation.

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

   C. Lynch syndrome is suspected in patients with colorectal cancer (see Policy Guidelines)

   D. Lynch syndrome is suspected in patients with endometrial cancer and either of the following:
      1. Patient is less than 50 years old at diagnosis; or
      2. One first-degree relative is diagnosed with a Lynch-associated cancer (see Policy Guidelines)

   E. Lynch syndrome is suspected in patients without colorectal cancer (including both cancer-free individuals and individuals with a Lynch-associated cancer other than colorectal cancer) but with a family history meeting either Amsterdam II or modified Amsterdam II criteria, when no affected family members have been tested for MMR or EPCAM mutations:
      1. **Amsterdam II criteria**: The family (from one lineage), including the index patient, must meet all of the following criteria:
         a. Three or more family members with a histologically-verified Lynch-associated cancer (see Policy Guidelines), one of whom is a first-degree relative of the other two; and
         b. Lynch-associated cancer involving at least two successive generations; and
2. **Modified Amsterdam II Criteria:** For very small families the modified Amsterdam II criteria may be applied. One of the following criteria must be met:
   
a. Two colorectal cancers in first-degree relatives involving at least two generations, with at least one individual diagnosed by age 55; or
   
b. 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.

II. 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 on immunohistochemical (IHC) analysis.

III. Genetic testing for Lynch and polyposis syndromes that does not meet the medical necessity criteria (I or II) is considered **investigational**, including but not limited to panel tests that include genes other than *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM*.

**POLICY GUIDELINES**

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutations being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing?
6. Medical records related to this genetic test
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided, if any

**Genes Associated with Lynch and Polyposis Syndromes:** Genes associated with Lynch and polyposis syndromes include the following: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* genes.

**Definition of At-risk Relatives:** *At risk relatives* refers to first-degree relatives (e.g., mother, father, sister, brother, children) of the patient.

**Lynch Associated Cancers:** Lynch-associated cancers include cancers of the colon/rectum, endometrium, stomach, ovary, pancreas, bladder, ureter, renal pelvis, biliary tract, brain (usually glioblastomas), sebaceous gland adenomas and keratoacanthomas, and small intestine.
Lynch Syndrome in Patients without Colorectal Cancer: Criterion I.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.

Patients with Colorectal Cancer: When tumor tissue is available for testing 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.

SCIENTIFIC EVIDENCE

FAP Genetic Testing

The policy for FAP genetic testing was based on a 1998 TEC Assessment[10], 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[11] and from several publications[12-16] 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[11] 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

Mismatch Repair (MMR) Genetic Testing

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[17], a supplemental assessment to that report contracted by the EGAPP Working Group[6], and an EGAPP recommendation for genetic testing in colorectal cancer.[7] 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.\textsuperscript{[18]} 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.[19] 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%[20] 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.[21] 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.[22] 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.[23] 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.[24] 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.[25-30] 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).[31]

**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.[4,32,33]

In 2013, Capper et al. reported on a technique of BRAF V600E-specific (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.[24] 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%[38]) 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%[22]). 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.[6]

In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome.[36] This study 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.

Several groups have recommended screening endometrial cancer patients for Lynch syndrome. At the 2010 Jerusalem Workshop on Lynch Syndrome it was proposed that all incident cases of endometrial cancer be screened for Lynch syndrome using MMR-IHC.[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.[31,40,41] 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]

Lynch Syndrome

The 2016 NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal recommend that all colorectal cancers should undergo tumor testing with MSI or IHC for the four MMR genes and EPCAM. Further risk assessment, genetic counseling, and possible genetic testing is recommended for those that meet one or more of the following criteria:

1. Meets revised Bethesda Guidelines
2. Meets Amsterdam II criteria
3. Endometrial cancer at age 50 or younger
4. Known Lynch syndrome in family
5. Consider testing individuals with ≥5% risk of Lynch syndrome based on one of the following mutation prediction models: MMRpro, PREMM, or MMR predict
The NCCN indicates that testing for all MMR genes and EPCAM vs. sequential or stepwise testing should be left to the discretion of the clinician. The NCCN guidelines also indicate that abnormal MLH1 expression by IHC should be followed by tumor BRAF V600E testing or MLH1 promoter methylation testing to exclude a diagnosis of Lynch syndrome. As noted in the NCCN guidelines, “BRAF V600E mutation tumor testing does not apply to endometrial cancer.”

Polypsis Syndrome

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 ≥20 adenomas or known deleterious mutations of either APC or MUTYH in the family. Additionally, they recommend considering genetic testing for those with a personal history of 10-20 adenomas or some adenomas and clinical indications of serrated polyposis syndrome, in order to differentiate AFAP from MAP or other types of colonic polyposis.

American College of Gastroenterology

The American College of Gastroenterology (ACG) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.[43]

Lynch Syndrome

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

Adenomatous polyposis syndromes

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

U.S. Multi-Society Task Force on Colorectal Cancer

In 2014, the Multi-Society Task Force published guidelines regarding Lynch syndrome testing and indicated, “the use of genetic panels might uncover patients and families with forms of attenuated polyposis, such as MYH-associated polyposis, attenuated familial adenomatous polyposis, and
polymerase proofreading polyposis; there is often blurring of the clinical presentations of these syndromes and LS (Lynch Syndrome).”[44]

Summary

There is enough research to show that genetic testing for $APC$, $MUTYH$, $MLH1$, $MSH2$, $MSH6$, $PMS2$, and $EPCAM$ can improve health outcomes for some cancer patients and their families. There are many clinical practice guidelines that recommend genetic testing for certain people at high risk for these colorectal cancer syndromes. Therefore, genetic testing for any combination of these genes mutations may be considered medically necessary when policy criteria are met.

There is enough research to show that tumor testing for a $BRAF$ V600E mutation can help to diagnose Lynch syndrome in patients with a particular type of colorectal tumor, which can improve health outcomes for patients and their families. Therefore, testing for $BRAF$ V600E or $MLH1$ promoter methylation may be considered medically necessary when policy criteria are met.

There is not enough research to show that genetic testing for Lynch and polyposis syndromes can improve risk assessment and lead to better health outcomes for patients when policy criteria are not met. This includes testing with panel tests that contains genes other than $APC$, $MUTYH$, $MLH1$, $MSH2$, $MSH6$, $PMS2$, and $EPCAM$. Therefore, genetic testing that does not meet the policy criteria, such as panel testing that include testing for genes other than $APC$, $MUTYH$, $MLH1$, $MSH2$, $MSH6$, $PMS2$, and $EPCAM$, is considered investigational.

REFERENCES


CROSS REFERENCES

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

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

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<td>CODES</td>
<td>NUMBER</td>
<td>DESCRIPTION</td>
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<td></td>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td></td>
<td>81293</td>
<td>; known familial variants</td>
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<td>81294</td>
<td>; duplication/deletion variants</td>
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<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81296</td>
<td>; known familial variants</td>
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<tr>
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<td>81297</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary duplication/deletion variants)</td>
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<tr>
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<td>81298</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81299</td>
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<td>81300</td>
<td>; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81301</td>
<td>Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
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<tr>
<td></td>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td></td>
<td>81318</td>
<td>; known familial variants</td>
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<td></td>
<td>81319</td>
<td>; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81435</td>
<td>Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosisis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11</td>
</tr>
<tr>
<td></td>
<td>81436</td>
<td>;duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11</td>
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<td>88363</td>
<td>Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)</td>
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<tr>
<td>HCPCS</td>
<td>None</td>
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