



## Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes

Effective: January 1, 2025

Next Review: October 2025

Last Review: December 2024

### 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

There are hereditary conditions that predispose affected individuals to colorectal cancer (CRC), including MUTYH-associated polyposis (MAP), 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).

### MEDICAL POLICY CRITERIA

**Note:** This policy only addresses testing for Lynch syndrome and APC-associated and MUTYH-associated polyposis syndromes.

- I. Genetic testing for *APC*, *MUTYH*, mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) and/or *EPCAM* gene variants may be considered **medically necessary** when any one of the following criteria 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* disease-

associated variant.

- 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 or endometrial cancer
- D. Lynch syndrome is suspected in patients *without* colorectal or endometrial cancer (including both cancer-free individuals and individuals with a Lynch-associated cancer other than colorectal or endometrial cancer, see below), when no affected family members have been tested for MMR or *EPCAM* variants, and one or more of the following is met:
  - 1. A first-degree relative with a colorectal or endometrial cancer diagnosed before age 50
  - 2. A first-degree relative with both of the following (a. and b.):
    - a. Colorectal or endometrial cancer; and
    - b. A second Lynch syndrome-associated cancer (cancer of the colon/rectum, endometrium, stomach, ovary, pancreas, bladder, ureter, renal pelvis, biliary tract, brain [usually glioblastomas], or small intestine, or a sebaceous adenoma, sebaceous carcinoma, or keratoacanthomas)
  - 3. Two or more first- or second-degree relatives (from the same side of the family) with Lynch syndrome-associated cancers, including one diagnosed before age 50
  - 4. Three or more first- or second-degree relatives (from the same side of the family) with Lynch syndrome-associated cancers
  - 5. Two colorectal cancers in first-degree relatives involving at least two generations, with at least one individual diagnosed by age 55
  - 6. Documentation of 5% or higher predicted risk of the syndrome on a risk prediction model, such as MMRpro, PREMM5, or MMRpredict
- II. Genetic testing for *BRAF* variants 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, APC-associated, and MUTYH-associated 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*.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

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- and second-degree relatives of the patient. First-degree relatives include an individual's parents, siblings, and children.

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), and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas.

Patients with Colorectal or Endometrial Cancer: When tumor tissue is available for testing either the microsatellite instability (MSI) test or the immunohistochemistry (IHC) test with or without *BRAF* gene variant testing should be used as an initial evaluation of tumor tissue prior to MMR gene analysis.

Risk Prediction Models: Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are available, such as MMRpro<sup>[1]</sup>, PREMM<sub>5</sub><sup>[2]</sup>, or MMRpredict<sup>[3]</sup>.

## LIST OF INFORMATION NEEDED FOR REVIEW

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 variants 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
  - o History and physical exam
  - o Conventional testing and outcomes
  - o Conservative treatment provided, if any

## CROSS REFERENCES

1. [Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening](#), Genetic Testing, Policy No. 12
2. [KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer](#), Genetic Testing, Policy No. 13
3. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
4. [BRAF Genetic Testing To Select Melanoma or Glioma Patients for Targeted Therapy](#), Genetic Testing, Policy No. 41
5. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64

## BACKGROUND

### 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 variants in the adenomatous polyposis coli (*APC*) gene, located on chromosome five, 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 variants in the *APC* gene as well. However, fewer than 30% of AFAP patients have *APC* variants and may have variants 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 variants in the *MUTYH* gene and is inherited in an autosomal recessive manner. Biallelic *MUTYH* variants are associated with a cumulative CRC risk of about 80% by age 70. Monoallelic *MUTYH* variant-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.<sup>[4, 5]</sup> These cancers are sometimes

collectively referred to as HNPCC- or Lynch syndrome-associated cancers. The syndrome is estimated to account for approximately 3% of colorectal and endometrial cancers.<sup>[6]</sup> 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 variants *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 Variants 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 variants in one of the several mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and rarely *MLH3*, *PSM1* and *EXO1*). Variants 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 variants in either *MLH1* or *MSH2*, and testing for MMR gene variants is often limited to these two genes. If results are negative, *MSH6* and *PMS2* genes may be tested for variants next. Large gene sizes and the difficulty of detecting variants 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 variants. 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 CRC in IHC *MLH1*-negative cases.<sup>[7]</sup> Therefore, *BRAF*-positive samples need not be further tested by *MLH1* sequencing.

### **Lynch Syndrome and Variants 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* variant 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.<sup>[6]</sup> In another words, these criteria aim to “establish the diagnosis of Lynch syndrome based upon familial clustering of HNPCC-related tumors.”<sup>[8]</sup> The revised Amsterdam II criteria are broader than Amsterdam I as they consider both colorectal and HNPCC-associated cancers in the assessment.<sup>[6]</sup> 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 CRC than strategies involving

the analysis of tumor samples (e.g., MSI, IHC).<sup>[9, 10]</sup> However, family history is still considered “an important component of cancer risk assessment in the general population”<sup>[10]</sup>

The Bethesda criteria were developed with a different purpose than the Amsterdam criteria.<sup>[4, 11]</sup> They were designed to “help predict which patients *with* colorectal cancer are likely to have a mismatch-repair variant and should thus undergo further testing.”<sup>[8]</sup>

## 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.

### Genetic Testing Panels

Sequencing of FAP, AFAP, MUTYH or Lynch syndrome variants 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.

## EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature<sup>[12]</sup> is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

## FAP GENETIC TESTING

The initial policy evidence for FAP genetic testing was based on a 1998 TEC Assessment<sup>[13]</sup>, 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* variant.
- The optimal testing strategy is to define the specific genetic variant in an affected family member and then test the unaffected family members to see if they have inherited the same variant.

The additional policy information on attenuated FAP and on MUTYH-associated polyposis diagnostic criteria and genetic testing is based on information from GeneReviews<sup>[14]</sup> and from several publications<sup>[15-19]</sup> that build on prior, cited research.

## 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 evidence for Lynch syndrome genetic testing in CRC patients was initially based on an evidence report published by the AHRQ<sup>[20]</sup>, a supplemental assessment to that report contracted by the EGAPP Working Group<sup>[9]</sup>, and an EGAPP recommendation for genetic testing in CRC.<sup>[10]</sup> Based on the AHRQ report and supplemental assessment, the EGAPP report came to the following conclusions regarding genetic testing for MMR variants in patients already diagnosed with CRC:

- Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for MMR 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 CRC 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 to 25 years was high at 53% to 100%.
    - One long-term, nonrandomized controlled study and one cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance vs. those who did not.
    - Surveillance, prevention for other Lynch syndrome cancers (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.<sup>[21]</sup> 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 CRC for MMR gene variants. 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 regarding benefits derived from patients with CRC 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 CRC and Lynch syndrome who choose prophylactic surgical treatment.

Early documentation of the natural history of CRC in highly selected families with a strong history of hereditary CRC indicated risks of synchronous and metachronous cancers as high as 18% and 24%<sup>[22]</sup> in patients who already had CRC. As a result, in 1996, the Cancer Genetic Studies Consortium, a temporary NIH-appointed body, recommended that if CRC is diagnosed in patients with an identified variant or a strong family history, a subtotal colectomy with ileorectal anastomosis (IRA) should be considered in preference to segmental resection.<sup>[23]</sup> Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. One 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.<sup>[24]</sup> 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.<sup>[25]</sup> 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 CRC, especially those who are younger.<sup>[26]</sup> 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.

Vos (2020) evaluated the yield to detect Lynch syndrome in a prospective cohort of 3,602 newly diagnosed CRC cases below age 70.<sup>[27]</sup> The standard testing protocol included IHC or MSI testing, followed by *MLH1* hypermethylation testing. Testing identified *MLH1* hypermethylation in a majority of cases tested (66% of 264). The percentage of MMR deficient CRC explained by hypermethylation increased with age, while the percentage of patients with hereditary CRC decreased with age. Of the 47 patients who underwent genetic testing, 55% (26/47) were determined to have Lynch syndrome. The authors estimated that only 78% of these cases would have been identified by the revised Bethesda guidelines. The percentage by age was 86% (6/7) in those under 40 years, 57% (17/29) in patients aged 40 to 64 years, and 30% (3/10) in patients 65 to 69 years of age and the number needed to test to identify one case of Lynch syndrome after prescreening was 1.2 (95% confidence interval [CI] 1.0 to 2.0) in patients under 40 years, 4.1 (95% CI 3.1 to 5.5) in patients 40 to 64 years of age, and 21 (95% CI 11 to 43) in CRC patients aged 65 to 69.

## ***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* variants with Lynch-like disease in families.<sup>[28-33]</sup> Because studies differ slightly in how patients were selected, prevalence of these *EPCAM* variants is difficult to estimate, but may be in the range of 20% to 40% of patients/families who meet Lynch syndrome criteria, do not have a MMR variant, but have MSI-high tumor tissue. Kempers (2011) reported that carriers of an *EPCAM* deletion had a 75% (95% CI 65 to 85) cumulative risk of CRC by age 70, not significantly different from that of carriers of an *MSH2* deletion (77%, 95% CI 64 to 90); mean age at diagnosis was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI 0 to 27) by age 70, compared to carriers of a variant in *MSH2* (51%, 95% CI 33 to 69,  $p=0.0006$ ).<sup>[34]</sup>

## ***BRAF* TESTING**

*BRAF* V600E 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 variant analysis for a Lynch syndrome diagnosis.<sup>[7, 35, 36]</sup>

Capper (2013) reported on a technique of *BRAF* V600E-specific (VE1) IHC testing for *BRAF* variants on a series of 91 MSI-H CRC patients.<sup>[37]</sup> 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 CRC who have completed childbearing or to women undergoing abdominal surgery for other conditions, especially when there is a family history of endometrial cancer.<sup>[26]</sup> This recommendation is based on the high rate of endometrial cancer in variant-positive individuals (30 to 64% in studies that may be biased by strong family history; overall, possibly as low as 20 to 25%<sup>[11]</sup>) and the lack of efficacy of screening.

The estimated the risk of endometrial cancer in variant carriers is 34% by age 70 (95% CI 17 to 60%), and of ovarian cancer is 8% by age 70 (95% CI 2 to 39%).<sup>[38]</sup> 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%).<sup>[24]</sup> 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.<sup>[9]</sup>

In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome.<sup>[39]</sup> This study estimated that for every 100 women diagnosed with Lynch syndrome-associated CRC, about 23 will be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Recent data on variant-specific risks suggests that prophylactic gynecological surgery benefits for carriers of *MSH6* variants may offer less obvious benefits compared to harms as lifetime risk of endometrial cancer is lower than for carriers of *MLH1* or *MSH2* variants, and lifetime risk of ovarian cancer is similar to the risk for the general population.<sup>[38]</sup> 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-IH.<sup>[40]</sup> Clarke and Cooper (2012) 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.<sup>[41]</sup> Kwon (2011) 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.<sup>[42]</sup>

However, in the case of *EPCAM* deletion carriers, three studies found three cases of endometrial cancer in 103 female carriers who did not undergo preventive hysterectomy.<sup>[34, 43, 44]</sup> Women with *EPCAM* deletions consequently have a life-time risk of developing endometrial cancer decreased by 10-fold when compared with MMR gene variant carriers. This might support a clinical management scenario rather than prophylactic surgery.<sup>[43]</sup>

## NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)<sup>[45]</sup>

### Lynch Syndrome

The NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (v.3.2024) recommend that all colorectal and endometrial cancers should undergo tumor testing with MSI and/or IHC for the four MMR genes and *EPCAM*.

The guidelines state that direct referral for germline genetic testing to rule out Lynch syndrome may be preferred in patients with a strong family history or if diagnosed before age 50.

Criteria that may justify Lynch syndrome testing according to this guideline are:

- A known Lynch syndrome variant in the family
- MMR deficiency on tumor testing
- Diagnosis of a Lynch syndrome-related cancer, and:
  - Cancer diagnosis prior to age 50, or
  - A synchronous or metachronous Lynch syndrome-related cancer, or
  - One first- or second-degree relative with a Lynch syndrome-related cancer diagnosed before age 50, or
  - Two or more first- or second-degree relatives with a Lynch syndrome-related cancer, regardless of age
- A family history of any of the following (on the same side of the family):
  - One or more first-degree relatives with colorectal or endometrial cancer diagnosed before age 50
  - One or more first-degree relatives with a colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-related cancer
  - Two or more first- or second-degree relatives with Lynch syndrome-related cancers, including at least one diagnosed before age 50
  - Three or more first- or second-degree relatives with Lynch syndrome-related cancers, regardless of age
- A >5% risk based on predictive models (e.g., MMRpro, PREMM5, or MMRpredict)

The guideline also indicated that abnormal *MLH1* expression by IHC in colorectal or endometrial cancers should be followed by tumor *MLH1* promoter methylation testing, or, for CRCs, testing for a *BRAF* V600E variant prior to genetic testing to exclude a diagnosis of Lynch syndrome. However, the guideline notes, “the absence of a *BRAF* V600E [pathogenic variant] does not rule out *MLH1* methylation.”

### Polyposis Syndrome

The NCCN guidelines also address familial adenomatous polyposis (classical and attenuated) and *MUTYH*-associated polyposis, and they recommend genetic testing for patients with a personal history of 20 or more adenomas, known familial pathogenic variants in adenomatous polyposis genes, or multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE). Additionally, they recommend considering genetic testing for those with a personal history of 10 to 19 adenomas, unilateral CHRPE, some adenomas and clinical indications of serrated polyposis syndrome, a personal history of other APC-associated cancers (desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer), or 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.<sup>[46]</sup>

### Lynch Syndrome

ACG recommends that all newly diagnosed CRCs 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* variant or hypermethylation of *MLH1*), a known family variant associated with LS, or a risk of  $\geq 5\%$  chance of LS based on risk prediction models should undergo genetic evaluation for LS. Genetic testing of patients with suspected LS should include germline variant 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 more than 10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes. Genetic testing of patients with suspected adenomatous polyposis syndromes should include *APC* and *MUTYH* gene variant analysis.

## 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).”<sup>[47]</sup>

## 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 variants may be considered medically necessary when policy criteria are met.

There is enough research to show that tumor testing for a *BRAF* variant 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* variants or *MLH1* promoter methylation may be considered medically necessary when policy criteria are met.

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There is not enough research to show that genetic testing for Lynch, APC-associated, and MUTYH-associated 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 includes testing for genes other than *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*, is considered investigational.

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## CODES

Codes	Number	Description
CPT	0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only)]
	0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure) (Use 0130U in conjunction with 81435, 0101U)
	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	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 (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	;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 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



Codes	Number	Description
	81317	PMS2 (postmeiotic segregation increased 2 [ <i>S. cerevisiae</i> ]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	;known familial variants
	81319	;duplication/deletion variants
	81401	Molecular pathology procedure, Level 2
	81406	Molecular pathology procedure, Level 7
	81435	Hereditary colon cancer-related disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants; genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
	81436	;duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
HCPCS	None	

**Date of Origin:** January 2012