FEP 2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Effective Date: April 15, 2018

Related Policies:
2.04.53 KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Description

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

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several Clinical Laboratory Improvement Amendments (CLIA)–licensed clinical laboratories offer MMR gene variant testing for Lynch syndrome. For example, the GeneTests website (available online at http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2622?db=genetests) lists 32 U.S.-located laboratories that offer this service. In at least 1 laboratory, Lynch syndrome variant testing is packaged under 1 copyrighted name. The COLARIS® test (Myriad Genetic Laboratories) includes sequence analysis of *MLH1*, *MSH2*, *MSH6*, and *PMS2*; large rearrangement analysis for *MLH1*, *MSH2*, *PMS2*, and *MSH6* large deletions/duplications; and analysis for large deletions in the *EPCAM* gene near *MSH2*. Note that there are 2 versions of this test, the COLARIS (excludes *PMS2* testing) and COLARIS Update (includes *PMS2* testing). Individualized testing (eg, targeted testing for a family variant) can also be requested. The COLARIS®^{PLUS} test includes full sequence analysis of *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *MYH* genes and rearrangement analysis of *MLH1*, *MSH2*, *MSH6*, *MYH*, and *EPCAM* by microarray comparative genomic hybridization analysis, and multiplex ligation–dependent probe amplification analysis for *PMS2.*

Similarly, GeneTests lists U.S.-based CLIA-licensed clinical laboratories that provide *APC* variant testing and those that provide *MUTYH* variant testing. The COLARIS® AP test (Myriad Genetic Laboratories) includes DNA sequencing analysis of the *APC* and *MUTYH* genes, as well as analysis of large rearrangements in the *APC* gene not detected by DNA sequencing.

Several Clinical Laboratory Improvement Amendments (CLIA)–licensed clinical laboratories offer MMR gene variant testing for Lynch syndrome. For example, the GeneTests website (available online at http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2622?db=genetests) lists 32 U.S.-located laboratories that offer this service. In at least 1 laboratory, Lynch syndrome variant testing is packaged under 1 copyrighted name. The COLARIS® test (Myriad Genetic Laboratories) includes sequence analysis of *MLH1*, *MSH2*, *MSH6*, and *PMS2*; large rearrangement analysis for *MLH1*, *MSH2*, *PMS2*, and *MSH6* large deletions/duplications; and analysis for large deletions in the *EPCAM* gene near *MSH2*. Note that there are 2 versions of this test, the COLARIS (excludes *PMS2* testing) and COLARIS Update (includes *PMS2* testing). Individualized testing (eg, targeted testing for a family variant) can also be requested. The COLARIS®^{PLUS} test includes full sequence analysis of *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *MYH* genes and rearrangement analysis of *MLH1*, *MSH2*, *MSH6*, *MYH*, and *EPCAM* by microarray comparative genomic hybridization analysis, and multiplex ligation–dependent probe amplification analysis for *PMS2.*

Similarly, GeneTests lists U.S.-based CLIA-licensed clinical laboratories that provide *APC* variant testing and those that provide *MUTYH* variant testing. The COLARIS® AP test (Myriad Genetic Laboratories) includes DNA sequencing analysis of the *APC* and *MUTYH* genes, as well as analysis of large rearrangements in the *APC* gene not detected by DNA sequencing.

POLICY STATEMENT

APC Testing

Genetic testing for *APC* gene variants may be considered **medically necessary** in the following patients:

- At-risk relatives (see Policy Guidelines section) of patients with familial adenomatous polyposis (FAP) and/or a known *APC* variant
- Patients with a differential diagnosis of attenuated FAP vs *MUTYH*-associated polyposis (MAP) vs Lynch syndrome. Whether testing begins with *APC* variants or screening for mismatch repair (MMR) variants depends on clinical presentation.

Genetic testing for *APC* gene variants is **not medically necessary** for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

MUTYH Testing

Genetic testing for *MUTYH* gene variants may be considered **medically necessary** in the following patients:

- Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome and a negative result for *APC* gene variants. A family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

MMR GENE Testing

Genetic testing for MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) may be considered **medically necessary** in the following patients:

- Patients with colorectal cancer (CRC), for the diagnosis of Lynch syndrome (see Policy Guidelines section).

- Patients with endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer (see Policy/Benefit Guidelines section), for the diagnosis of Lynch syndrome.
- At-risk relatives (see Policy/Benefit Guidelines section) of patients with Lynch syndrome with a known MMR gene variant.
- Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. Whether testing begins with *APC* variants or screening for MMR genes depends on clinical presentation.
- Patients without CRC (see Policy/Benefit Guidelines section) but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR variants.

EPCAM Testing

Genetic testing for *EPCAM* gene variants may be considered **medically necessary** when any one of the following 3 major criteria (solid bullets) is met:

- Patients with CRC, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when:
  - Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for a *MSH2* germline variant; OR
  - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in *MSH2*, *MLH1*, *PMS2*, *and MSH6*; OR
- At-risk relatives (see Policy/Benefit Guidelines section) of patients with Lynch syndrome with a known *EPCAM* variant; OR
- Patients without CRC but with a family history (see Policy/Benefit Guidelines section) meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR variants, and when sequencing for MMR variants is negative.

BRAF V600E or *MLH1* promoter methylation

Genetic testing for *BRAF* V600E or *MLH1* promoter methylation may be considered **medically necessary** to exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a CRC tumor on immunohistochemical analysis.

Genetic Counseling

Pre- and posttest genetic counseling (see Policy/Benefit Guidelines section) may be considered **medically necessary** as an adjunct to the genetic testing itself.

Genetic testing for all other gene variants for Lynch syndrome or CRC is considered **investigational**.

POLICY GUIDELINES

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Evaluation for Lynch Syndrome

For patients with colorectal cancer (CRC) being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test or the immunohistochemical (IHC) test with or without *BRAF* gene variant testing, should be used as an initial evaluation of tumor tissue before mismatch repair (MMR) gene analysis. Both

tests are not necessary. Proceeding to MMR gene sequencing would depend on results of MSI or IHC testing. In particular, IHC testing may help direct which MMR gene likely contains a variant, if any, and may also provide additional information if MMR genetic testing is inconclusive.

When indicated, genetic sequencing for MMR gene variants should begin with *MLH1* and *MSH2* genes, unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications; when MMR gene variants are expected based on IHC or MSI studies, but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

The Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families (Umar et al, 2004). The Bethesda guidelines are also considered more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

- CRC diagnosed in a patient who is less than 50 years old;
- Presence of synchronous or metachronous CRC or other HNPCC–associated tumors,* regardless of age;
- CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old;
- CRC diagnosed in 1 or more first-degree relatives with a Lynch syndrome–associated tumor, with one of the cancers being diagnosed at younger than 50 years of age;
- CRC diagnosed in 2 or more first or second-degree relatives with HNPCC-related tumors,* regardless of age.

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), sebaceous bland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are currently available such MMRpro, PREMM5 (Kastrinos et al, 2017), or MMRpredict. National Comprehensive Cancer Network guidelines recommend (category 2A) testing for Lynch syndrome genetic for individuals with a 5% or higher predicted risk of Lynch syndrome on these risk prediction models.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

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

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, or (2) have colon cancer, or (3) have endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, or (4) are at-risk relatives of patients with Lynch syndrome, or (5) are without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria who receive genetic testing for MMR genes, the evidence includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in CRC. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known variant in an MMR gene, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study

and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who did and did not follow recommended colonic surveillance. A positive genetic test for an MMR variant can also lead to changes in the management of other Lynch syndrome malignancies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have CRC in whom MLH1 protein is not expressed on immunohistochemical analysis who receives genetic testing for *BRAF* V600E or *MLH1* promoter methylation, the evidence includes a few case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between *BRAF* V600E variant and *MLH1* promoter methylation with sporadic CRC. Therefore, this type of testing could eliminate the need for further genetic testing or counseling for Lynch syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

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

Evaluation of Genomic Applications in Practice and Prevention recommendations noted that the current evidence is insufficient to clearly support benefit from genetic testing to the index patient with CRC if found to have Lynch syndrome. However, professional societies have reviewed the evidence and concluded that genetic testing likely has direct benefits for at least some patients with CRC and Lynch syndrome by differing recommendations for postsurgical surveillance, and for those who choose prophylactic surgical treatment instead of surveillance. NCCN guidelines for colon cancer (v.2.2017)[79] and for CRC screening (v.1.2017)[80] recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year postsurgery and, if normal, again in 3 years, then every 5 years based on findings. However, because of the high likelihood of cancer, colonoscopy is recommended every 1 to 2 years throughout life for patients with Lynch syndrome before cancer diagnosis; and the high likelihood of a second primary cancer is based on a first cancer diagnosis.[66] NCCN guidelines on genetic/familial high-risk assessment for colorectal indicate for *MLH1*, *MSH2*, and *EPCAM* variant carriers that surveillance with colonoscopy should begin “at age 20 to 25 years or 2 to 5

years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years."[77] "*MSH6* variant carriers should begin surveillance with colonoscopy at age 30 to 35 years, and *PMS2* carriers should begin surveillance at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 years for *MSH6* and *PMS2* variant carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years." "If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered."

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

American College of Gastroenterology

The American College of Gastroenterology issued practice guidelines (2015) for the management of patients with hereditary gastrointestinal cancer syndromes.[81]

Lynch syndrome (LS)

- "All newly diagnosed colorectal cancers should be evaluated for mismatch repair deficiency.
- "Analysis may be done by immunohistochemical (IHC) testing for the *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 ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.[82]
- "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

"Familial adenomatous polyposis (FAP)/MUTYH-associated polyposis/attenuated polyposis

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

American Society of Clinical Oncology and Society of Surgical Oncology

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

- "Tumor testing ***for DNA mismatch repair (MMR) deficiency*** with immunohistochemistry for MMR proteins and/or MSI should be ***assessed*** in all CRC patients. As an alternate strategy,

tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines.

- If loss of MLH1/PMS2 ***protein expression*** is observed in the tumor, analysis of *BRAF* V600E mutation or analysis of methylation of the *MLH1* promoter should be carried out first to rule out a sporadic case. ***If tumor is MMR deficient and somatic* BRAF *mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated***.
- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out ***for the genes corresponding to the absent proteins* (eg, MSH2, MSH6, EPCAM, PMS2, or MLH1).**
- Full germline genetic testing ***for Lynch syndrome*** should include DNA sequencing and large rearrangement analysis…
- Patients with multiple colorectal adenomas should be considered for full germline genetic testing of *APC* and/or *MUTYH*."
- Germline testing of *MUTYH* can be initiated by screening for the most common mutations (*G396D, Y179C*) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. ***For nonwhite individuals, full sequencing of* MUTYH *should be considered***."

U.S. Preventive Services Task Force Recommendations

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

Medicare National Coverage

Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (ie, clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. Centers for Medicare & Medicaid Services recognizes Lynch syndrome as "an autosomal dominant syndrome that accounts for about 3% to 5% of colorectal cancer cases. [Lynch] syndrome variants occur in the following genes: *hMLH1*, *hMSH2*, *hMSH6*, *PMS2*, and *EPCAM*." The Centers for Medicare & Medicaid Services also recognize FAP and MAP syndromes and their associated variants.

REFERENCES

1. Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology.* Dec 2009;137(6):1976-1985 e1971-1910. PMID 19732775
2. Balmana J, Castells A, Cervantes A. Familial colorectal cancer risk: ESMO Clinical Practice Guidelines. *Ann Oncol.* May 2010;21 Suppl 5:v78-81. PMID 20555108
3. Gala M, Chung DC. Hereditary colon cancer syndromes. *Semin Oncol.* Aug 2011;38(4):490-499. PMID 21810508
4. Quehenberger F, Vasen HF, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. *J Med Genet.* Jun 2005;42(6):491-496. PMID 15937084
5. Guindalini RS, Win AK, Gulden C, et al. Mutation spectrum and risk of colorectal cancer in African American families with Lynch syndrome. *Gastroenterology.* Nov 2015;149(6):1446-1453. PMID 26248088
6. Sinn DH, Chang DK, Kim YH, et al. Effectiveness of each Bethesda marker in defining microsatellite instability when screening for Lynch syndrome. *Hepatogastroenterology.* May-Jun 2009;56(91-92):672-676. PMID 19621678
7. Wu Y, Berends MJ, Mensink RG, et al. Association of hereditary nonpolyposis colorectal cancer-related tumors displaying low microsatellite instability with MSH6 germline mutations. *Am J Hum Genet.* Nov 1999;65(5):1291-1298. PMID 10521294

8. Goel A, Nagasaka T, Spiegel J, et al. Low frequency of Lynch syndrome among young patients with non-familial colorectal cancer. *Clin Gastroenterol Hepatol.* Nov 2010;8(11):966-971. PMID 20655395
9. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med.* Jan 2009;11(1):42-65. PMID 19125127
10. Bouzourene H, Hutter P, Losi L, et al. Selection of patients with germline MLH1 mutated Lynch syndrome by determination of MLH1 methylation and BRAF mutation. *Fam Cancer.* Jun 2010;9(2):167-172. PMID 19949877
11. Niessen RC, Hofstra RM, Westers H, et al. Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. *Genes Chromosomes Cancer.* Aug 2009;48(8):737-744. PMID 19455606
12. Kloor M, Voigt AY, Schackert HK, et al. Analysis of EPCAM protein expression in diagnostics of Lynch syndrome. *J Clin Oncol.* Jan 10 2011;29(2):223-227. PMID 21115857
13. Kuiper RP, Vissers LE, Venkatachalam R, et al. Recurrence and variability of germline EPCAM deletions in Lynch syndrome. *Hum Mutat.* Apr 2011;32(4):407-414. PMID 21309036
14. Kovacs ME, Papp J, Szentirmay Z, et al. Deletions removing the last exon of TACSTD1 constitute a distinct class of mutations predisposing to Lynch syndrome. *Hum Mutat.* Feb 2009;30(2):197-203. PMID 19177550
15. Ligtenberg MJ, Kuiper RP, Chan TL, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. *Nat Genet.* Jan 2009;41(1):112-117. PMID 19098912
16. Rumilla K, Schowalter KV, Lindor NM, et al. Frequency of deletions of EPCAM (TACSTD1) in MSH2-associated lynch syndrome cases. *J Mol Diagn.* Jan 2011;13(1):93-99. PMID 21227399
17. Hesson LB, Hitchins MP, Ward RL. Epimutations and cancer predisposition: importance and mechanisms. *Curr Opin Genet Dev.* Jun 2010;20(3):290-298. PMID 20359882
18. Hitchins MP. Inheritance of epigenetic aberrations (constitutional epimutations) in cancer susceptibility. *Adv Genet.* 2010;70:201-243. PMID 20920750
19. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology.* Jun 1999;116(6):1453-1456. PMID 10348829
20. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst.* Feb 18 2004;96(4):261-268. PMID 14970275
21. Kastrinos F, Uno H, Ukaegbu C, et al. Development and validation of the PREMM5 model for comprehensive risk assessment of Lynch syndrome. *J Clin Oncol.* Jul 01 2017;35(19):2165-2172. PMID 28489507
22. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Genetic Testing for Inherited Susceptibility to Colorectal Cancer: Part I – Adenomatous Polyposis Coli Gene Mutations. *TEC Assessments.* 1998;Volume 13:Tab 10.
23. Jasperson KW, Patel SG, Ahnen DJ. APC-Associated Polyposis Conditions. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2017.
24. Kastrinos F, Syngal S. Recently identified colon cancer predispositions: MYH and MSH6 mutations. *Semin Oncol.* Oct 2007;34(5):418-424. PMID 17920897
25. Lefevre JH, Parc Y, Svrcek M, et al. APC, MYH, and the correlation genotype-phenotype in colorectal polyposis. *Ann Surg Oncol.* Apr 2009;16(4):871-877. PMID 19169759
26. Avezzu A, Agostini M, Pucciarelli S, et al. The role of MYH gene in genetic predisposition to colorectal cancer: another piece of the puzzle. *Cancer Lett.* Sep 18 2008;268(2):308-313. PMID 18495334
27. Balaguer F, Castellvi-Bel S, Castells A, et al. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case-control, population-based study. *Clin Gastroenterol Hepatol.* Mar 2007;5(3):379-387. PMID 17368238
28. Lagarde A, Rouleau E, Ferrari A, et al. Germline APC mutation spectrum derived from 863 genomic variations identified through a 15-year medical genetics service to French patients with FAP. *J Med Genet.* Oct 2010;47(10):721-722. PMID 20685668
29. Aretz S, Stienen D, Uhlhaas S, et al. Large submicroscopic genomic APC deletions are a common cause of typical familial adenomatous polyposis. *J Med Genet.* Feb 2005;42(2):185-192. PMID 15689459
30. Bunyan DJ, Eccles DM, Sillibourne J, et al. Dosage analysis of cancer predisposition genes by multiplex ligation-dependent probe amplification. *Br J Cancer.* Sep 13 2004;91(6):1155-1159. PMID 15475941

31. Aretz S, Genuardi M, Hes FJ. Clinical utility gene card for: MUTYH-associated polyposis (MAP), autosomal recessive colorectal adenomatous polyposis, multiple colorectal adenomas, multiple adenomatous polyps (MAP) - update 2012. *Eur J Hum Genet.* Jan 2013;21(1). PMID 22872101
32. Inra JA, Steyerberg EW, Grover S, et al. Racial variation in frequency and phenotypes of APC and MUTYH mutations in 6,169 individuals undergoing genetic testing. *Genet Med.* Oct 2015;17(10):815-821. PMID 25590978
33. Out AA, Tops CM, Nielsen M, et al. Leiden Open Variation Database of the MUTYH gene. *Hum Mutat.* Nov 2010;31(11):1205-1215. PMID 20725929
34. Nielsen M, Lynch H, Infante E, et al. MUTYH-Associated Polyposis. In: Pagon RA, Adam MP, Ardinger HH, eds. *GeneReviews* Seattle, WA: University of Washington; 2012.
35. Sieber OM, Lamlum H, Crabtree MD, et al. Whole-gene APC deletions cause classical familial adenomatous polyposis, but not attenuated polyposis or "multiple" colorectal adenomas. *Proc Natl Acad Sci U S A.* Mar 05 2002;99(5):2954-2958. PMID 11867715
36. Aretz S, Uhlhaas S, Goergens H, et al. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. *Int J Cancer.* Aug 15 2006;119(4):807-814. PMID 16557584
37. Michils G, Tejpar S, Thoelen R, et al. Large deletions of the APC gene in 15% of mutation-negative patients with classical polyposis (FAP): a Belgian study. *Hum Mutat.* Feb 2005;25(2):125-134. PMID 15643602
38. Truta B, Allen BA, Conrad PG, et al. A comparison of the phenotype and genotype in adenomatous polyposis patients with and without a family history. *Fam Cancer.* 2005;4(2):127-133. PMID 15951963
39. Vasen HF, Griffioen G, Offerhaus GJ, et al. The value of screening and central registration of families with familial adenomatous polyposis. A study of 82 families in The Netherlands. *Dis Colon Rectum.* Mar 1990;33(3):227-230. PMID 2155763
40. Bjork JA, Akerbrant HI, Iselius LE, et al. Risk factors for rectal cancer morbidity and mortality in patients with familial adenomatous polyposis after colectomy and ileorectal anastomosis. *Dis Colon Rectum.* Dec 2000;43(12):1719-1725. PMID 11156457
41. Jarvinen HJ. Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival. *Gut.* Mar 1992;33(3):357-360. PMID 1314763
42. Bonis PA, Trikalinos TA, Chung M, et al. *Hereditary Nonpolyposis Colorectal Cancer: Diagnostic Strategies and Their Implications (Evidence Report/Technology Assessment No. 150, AHRQ Publication No. 07-E008).* Rockville, MD: Agency for Healthcare Research and Quality; 2007.
43. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med.* Jan 2009;11(1):35-41. PMID 19125126
44. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. *JAMA.* Oct 17 2012;308(15):1555-1565. PMID 23073952
45. Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. *Lancet Oncol.* Jan 2011;12(1):49-55. PMID 21145788
46. Jin M, Hampel H, Zhou X, et al. BRAF V600E mutation analysis simplifies the testing algorithm for Lynch syndrome. *Am J Clin Pathol.* Aug 2013;140(2):177-183. PMID 23897252
47. Capper D, Voigt A, Bozukova G, et al. BRAF V600E-specific immunohistochemistry for the exclusion of Lynch syndrome in MSI-H colorectal cancer. *Int J Cancer.* Oct 1 2013;133(7):1624-1630. PMID 23553055
48. Kastrinos F, Syngal S. Screening patients with colorectal cancer for Lynch syndrome: what are we waiting for? *J Clin Oncol.* Apr 1 2012;30(10):1024-1027. PMID 22355054
49. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA.* Jun 8 2011;305(22):2304-2310. PMID 21642682
50. Leenen CH, van Lier MG, van Doorn HC, et al. Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer </= 70 years. *Gynecol Oncol.* May 2012;125(2):414-420. PMID 22306203
51. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med.* May 05 2005;352(18):1851-1860. PMID 15872200
52. Aktan-Collan K, Mecklin JP, Jarvinen H, et al. Predictive genetic testing for hereditary non-polyposis colorectal cancer: uptake and long-term satisfaction. *Int J Cancer.* Jan 20 2000;89(1):44-50. PMID 10719730

53. Aktan-Collan K, Haukkala A, Pylvanainen K, et al. Direct contact in inviting high-risk members of hereditary colon cancer families to genetic counselling and DNA testing. *J Med Genet.* Nov 2007;44(11):732-738. PMID 17630403
54. Stanley AJ, Gaff CL, Aittomaki AK, et al. Value of predictive genetic testing in management of hereditary non-polyposis colorectal cancer (HNPCC). *Med J Aust.* Apr 03 2000;172(7):313-316. PMID 10844916
55. Hadley DW, Jenkins J, Dimond E, et al. Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. *Arch Intern Med.* Mar 10 2003;163(5):573-582. PMID 12622604
56. Lerman C, Hughes C, Trock BJ, et al. Genetic testing in families with hereditary nonpolyposis colon cancer. *JAMA.* May 05 1999;281(17):1618-1622. PMID 10235155
57. Codori AM, Petersen GM, Miglioretti DL, et al. Attitudes toward colon cancer gene testing: factors predicting test uptake. *Cancer Epidemiol Biomarkers Prev.* Apr 1999;8(4 Pt 2):345-351. PMID 10207639
58. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med.* Jan 19 2006;354(3):261-269. PMID 16421367
59. Fitzgibbons RJ, Jr., Lynch HT, Stanislav GV, et al. Recognition and treatment of patients with hereditary nonpolyposis colon cancer (Lynch syndromes I and II). *Ann Surg.* Sep 1987;206(3):289-295. PMID 3632093
60. Burke W, Petersen G, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. *JAMA.* Mar 19 1997;277(11):915-919. PMID 9062331
61. Van Dalen R, Church J, McGannon E, et al. Patterns of surgery in patients belonging to amsterdam-positive families. *Dis Colon Rectum.* May 2003;46(5):617-620. PMID 12792437
62. de Vos tot Nederveen Cappel WH, Buskens E, van Duijvendijk P, et al. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. *Gut.* Dec 2003;52(12):1752-1755. PMID 14633956
63. Guillem JG, Wood WC, Moley JF, et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. *J Clin Oncol.* Oct 1 2006;24(28):4642-4660. PMID 17008706
64. Järvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology.* May 1995;108(5):1405-1411. PMID 7729632
65. Järvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology.* May 2000;118(5):829-834. PMID 10784581
66. de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, et al. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. *Dis Colon Rectum.* Dec 2002;45(12):1588-1594. PMID 12473880
67. Dove-Edwin I, Sasieni P, Adams J, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. *BMJ.* Nov 05 2005;331(7524):1047. PMID 16243849
68. Järvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. *J Clin Oncol.* Oct 01 2009;27(28):4793-4797. PMID 19720893
69. Syngal S, Weeks JC, Schrag D, et al. Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. *Ann Intern Med.* Nov 15 1998;129(10):787-796. PMID 9841584
70. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol.* Feb 2010;8(2):174-182. PMID 19835992
71. Yurgelun MB, Mercado R, Rosenblatt M, et al. Impact of genetic testing on endometrial cancer risk-reducing practices in women at risk for Lynch syndrome. *Gynecol Oncol.* Dec 2012;127(3):544-551. PMID 22940489
72. Kwon JS, Scott JL, Gilks CB, et al. Testing women with endometrial cancer to detect Lynch syndrome. *J Clin Oncol.* Jun 1 2011;29(16):2247-2252. PMID 21537049
73. Obermair A, Youlden DR, Young JP, et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. *Int J Cancer.* Dec 1 2010;127(11):2678-2684. PMID 20533284
74. Grandval P, Baert-Desurmont S, Bonnet F, et al. Colon-specific phenotype in Lynch syndrome associated with EPCAM deletion. *Clin Genet.* Jul 2012;82(1):97-99. PMID 22243433
75. Lynch HT, Riegert-Johnson DL, Snyder C, et al. Lynch syndrome-associated extracolonic tumors are rare in two extended families with the same EPCAM deletion. *Am J Gastroenterol.* Oct 2011;106(10):1829-1836. PMID 21769135

76. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. *Acta Obstet Gynecol Scand.* May 2011;90(5):437-444. PMID 21306348
77. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2017. http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed August 1, 2017.
78. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. Version 3.2017. http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed August 1, 2017.
79. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2017. http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 1, 2017.
80. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening. Version 1.2017. http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Accessed August 1, 2017.
81. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol.* Feb 2015;110(2):223-262; quiz 263. PMID 25645574
82. Kastrinos F, Steyerberg EW, Mercado R, et al. The PREMM(1,2,6) model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. *Gastroenterology.* Jan 2011;140(1):73-81. PMID 20727894
83. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. *J Clin Oncol.* Jan 10 2015;33(2):209-217. PMID 25452455

POLICY HISTORY

Date	Action	Description
March 2012	New Policy	
March 2013	Update Policy	Policy updated with name change and literature review; References 15, 30, 43-49, 52, 53 added. Additional medically necessary indication added for patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer.
March 2014	Update Policy	Updated with literature review through September 2013. References 24, 33-35 and 58 added. References 39-40 updated. Policy Statement added that BRAF V600E or MLH1 promoter methylation may be considered medically necessary when MLH1 is not expressed in the tumor on IHC analysis.
December 2016	Update Policy	Policy updated with literature review through December 29, 2015; references 59-60 added. Policy statements unchanged.
December 2017	Update Policy	Policy updated with literature review through July 21, 2017; references 4-6, 28-33, 35-39, 41, 51-57, 64-65, 67-70, 83 added.
March 2018	Administrative Update	Corrected related policies number from 2.0.53 to 2.04.53 KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer.