

Medical Coverage Policy



Genetic Testing for Lynch Syndrome and Other Inherited Intestinal Polyposis Syndromes- PREAUTH

Device/Equipment Drug Medical Surgery Test Other

Effective Date:	7/1/2011	Policy Last Updated:	2/5/2013
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Prospective review is recommended/required. Please check the member agreement for preauthorization guidelines.

Prospective review is not required.

Description:

Genetic mutations have been identified as the cause of inherited cancer risk in some families with a history of colon cancer. There are currently **two well-defined types of hereditary colorectal cancer**:

- Familial adenomatous polyposis (FAP)
- Lynch syndrome, also called hereditary nonpolyposis colorectal cancer (HNPCC). Lynch syndrome has been implicated in some endometrial cancers as well.

Familial Adenomatous Polyposis (FAP)

Individuals with FAP almost always develop hundreds or even thousands of colorectal polyps at a very early age. Germline mutations in the adenomatous polyposis coli (APC) gene are responsible for FAP and are inherited in an autosomal dominant manner (abnormal gene coming from one parent).

A subset of FAP patients may have attenuated FAP (AFAP), characterized by 10-99 cumulative colorectal adenomas occurring later in life than in classical FA. It is generally accepted that genetic testing for FAP and AFAP is appropriate to confirm the diagnosis FAP and AFAP in an affected patient; as a predictive test for at-risk relatives of AFAP and FAP-affected patients with known APC gene mutation.

AFAP patients may have gene mutations in the MUTYH gene and are then diagnosed with MUTYH-associated polyposis (MAP). While clinical features of MAP are similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH mutations are associated with a cumulative colorectal cancer risk by age 70, whereas monoallelic MUTYH mutation-associated risk of colorectal cancer appears to be relatively minimal. When relatively few (i.e., between 10 and 99) adenomas are present and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include APC, MUTYH if APC is negative for mutations, and screening for mutations associated with Lynch syndrome. Genetic testing for mutations in the MUTYH gene is appropriate for specific subset of individuals who have been identified as at high-risk for MAP. Testing of MUTYH is indicated for diagnosis and calculation of the level of risk in relatives.

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

Lynch Syndrome (HNPCC)

Patients with Lynch syndrome have a predisposition to colorectal, and other malignancies* including endometrial cancer as a result of an inherited mutation in a DNA mismatch repair (MMR) gene. Lynch syndrome is associated with any of a large number of possible mutations in 1 of 4 MMR genes, known as MLH1, MSH2, MSH6, and PMS2 and rarely MLH3. Testing for MMR gene mutations is often limited to MLH1 and MSH2 and, sometimes, MSH6. Gene sizes and the difficulty of detecting mutations in these genes make direct sequencing a time- and cost-consuming process.

***Note: Lynch syndrome related cancers include: colorectal, endometrial, ovarian, gastric, hepatobiliary, small bowel cancer, pancreatic or transitional cell cancer of the renal pelvis or ureter and its association with colon cancer developing in people younger than 50 years of age.**

Although germline mutations in MMR genes are rarely found in young patients without an extended family history, restricting testing to those meeting the Amsterdam criteria** will miss cases of HNPCC in those with a small family size or an unknown family history. The Bethesda guidelines*** are broader and do not rely exclusively on family history. The original Bethesda guidelines are the most sensitive clinical criteria for identification of HNPCC patients (approximately 94 percent), but are the least specific (approximately 25 percent); thus, additional indirect screening methods are needed to determine which patients should precede to direct sequencing for MMR gene mutations.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommended testing all newly diagnosed patients with colorectal cancer for Lynch syndrome, using a screening strategy based on microsatellite instability (MSI) or immunohistochemical analysis (IHC [+BRAF]) followed by sequencing in screen-positive patients. In certain situations it is recommended that rather than starting with a blood test, HNPCC testing begin with molecular tests on tumor samples from affected family members. Two such tests are MSI and abnormal MMR protein via IHC in tumor cells. The most common of these is MSI testing. If these MSI tests are abnormal, a patient is more likely to have HNPCC and the patient can go on to have blood testing to look for a mutation in an HNPCC-related gene.

Recently, novel deletions have been reported to affect the expression of the MSH2 MMR gene in the absence of a MSH2 gene mutation, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule are responsible. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and IHC shows a lack of MSH2 expression, but no MSH2 mutation is found by sequencing.

Medical criteria:

- **Familial Adenomatous Polyposis (FAP)**

Genetic testing for APC gene mutations may be considered medically **necessary** when patient meets **ONE** of the following:

- At-risk relatives* of patients with FAP and/or a known APC mutation; **OR**
- Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation.

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

- **MUTYH gene mutation**

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

- a negative result for APC gene mutations; **AND**
One of the following

- Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome **OR**
- Individuals with personal history of adenomatous polyposis whose family history is consistent with MUTYH-associated polyposis (autosomal recessive).

- **Lynch Syndrome (HNPCC)**

Genetic testing for MMR gene mutations is considered medically necessary when patients meet **ONE** following criteria is met: in the following patients:

- Patients with HNPCC related cancer, for the diagnosis of Lynch syndrome (see Guidelines below); **OR**
- At-risk relatives* of patients with Lynch syndrome with a known MMR mutation; **OR**
- Patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer (see Guidelines), for the diagnosis of Lynch syndrome.
- Patients with a differential diagnosis of attenuated FAP (AFAP) vs. MUTYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation; **OR**
- Patients without colorectal cancer but with a family history meeting the Amsterdam* or Revised Bethesda** criteria, when no affected family members have been tested for MMR mutations.

Genetic testing for EPCAM mutations is considered medically necessary when any **one** of the following 3 major criteria are met:

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

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

Guidelines:

For patients with colorectal cancer being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test, or the immunohistochemistry (IHC) test with or without *BRAF* gene mutation testing, should be used as an initial evaluation of tumor tissue prior to MMR gene analysis. Both tests are not necessary. Consideration of proceeding to MMR gene sequencing would depend on the results of the MSI or IHC testing. IHC testing in particular may help direct which MMR gene likely contains a mutation, if any, and may also provide some additional information if MMR gene testing is inconclusive.

*At-risk refers to first-degree relatives defined as a blood relative with whom an individual shares approximately 50% of his/her genes including the individual's parents, full siblings and children. Judgment must be allowed in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.

Genetic testing to determine the carrier status of the HNPCC gene is **covered** in patients without a history of colorectal cancer but who have a first- or second-degree relative with a known HNPCC

mutation. Proceeding directly to genetic testing for HNPCC-related mutations may also be medically necessary in patients meeting the Amsterdam II criteria.

****Amsterdam II Clinical Criteria:**

Three or more relatives with a histologically verified HNPCC-associated cancer (colorectal, endometrial, ovarian, gastric, hepatobiliary, small bowel cancer, pancreatic or transitional cell cancer of the renal pelvis or ureter); and **ALL** of the following criteria should be present:

- One of whom is a first-degree relative of the other two; **AND**
- HNPCC-associated cancer involving at least two generations; **AND**
- Cancer in one or more affected relatives diagnosed before 50 years of age; **AND**
- Familial adenomatous polyposis (FAP) excluded in any cases of colorectal cancer; **AND**
- Tumors should be verified whenever possible.

Modifications allow for small HNPCC families:

- These families must have two colorectal cancers in first-degree relatives involving at least two generations, with at least one individual diagnosed by age 55; **OR**
- In families with 2 first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

*****Revised Bethesda Criteria:**

Individuals must meet **ONE** of the following criteria:

- Individuals diagnosed with colorectal cancer before age 50; **OR**
- Individuals with HNPCC-related cancer, including synchronous and metachronous colorectal cancers or associated extracolonic cancers regardless of age; **OR**
- Individuals with colorectal cancer with the MSI-H histology diagnosed in a patient **less than age 60; OR**
- Individuals with colorectal cancer and one or more first-degree relatives with colorectal cancer and/or HNPCC-related extracolonic cancer; if one of the cancers was diagnosed at age <50 years; **OR**
- Individuals with colorectal cancer and colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age. Lynch-related tumors include: endometrial, stomach, ovarian, cervical, esophageal, leukemia, thyroid, bladder, ureter, and renal pelvis, biliary tract, small bowel, breast, pancreas, liver, larynx, bronchus, lung, and brain (glioblastoma), sebaceous gland adenomas, and keratoacanthomas.

Policy:

Preauthorization is required for BlueCHiP for Medicare and recommended for all other BCBSRI products.

Genetic testing for inherited susceptibility to colon cancer is covered when patient meets the medical criteria above.

Coverage:

BlueCHiP for Medicare

Medicare excludes all screening (not just genetic screening) with certain statutory exceptions. BlueCHiP for Medicare provides no additional benefits for genetic screening. **Only** if the patient exhibits signs or symptoms of the disease would the test be not considered screening.

Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage, Subscriber Agreement, or Benefit Booklet, for applicable "Genetic Testing" coverage.

Coding:

Claims submitted by proprietary test name (e.g., Colaris or ColarisAP) without CPT codes may be subject to review.

The following HCPCS codes: Prior authorization is required for BlueCHiP for Medicare and recommended for all other BCBSRI products:

- S3828** Complete gene sequence analysis; MLH1 gene
- S3829** Complete gene sequence analysis; MLH2 gene
- S3830** Complete MLH1 and MLH2 gene sequence analysis for HNPCC genetic testing
- S3831** Single-mutation analysis (in individual with a known MLH1 and MLH2 mutation in the family) for HNPCC genetic testing
- S3833** Complete APC gene sequence analysis for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP
- S3834** Single-mutation analysis (history known APC mutation in the family) for susceptibility to FAP and attenuated FAP

The following CPT codes Prior authorization is required for BlueCHiP for Medicare and recommended for all other BCBSRI products.

- 81201**
- 81202**
- 81203**

The following genetic testing codes for commercial products will be subject to medical review. For BlueCHiP for Medicare these codes will be invalid, use the 2011 “stacking codes”:

- 81292**
- 81293**
- 81294**
- 81295**
- 81296**
- 81297**
- 81298**
- 81299**
- 81300**
- 81301**
- 81317**
- 81318**
- 81319**

Also known as:

FAP
HNPCC

Related topics:

Genetic testing

https://www.bcbsri.com/sites/default/files/polices/GeneticTestingA_0.pdf

Genetic counseling

<https://www.bcbsri.com/sites/default/files/polices/genetic-counseling-080612.pdf>

Published:

Provider Update, April 2013
Provider Update, May 2012
Provider Update, June 2011
Provider Update, June 2010
Provider Update, November 2009
Provider Update, November 2008
Policy Update, January 2008

Policy Update, August 2006
Policy Update, July 2001

Public Policy Description

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Harvard Medical School and Partners Healthcare. MLH1, MSH2, and MSH6 Sequencing and Deletion/Duplication Analysis for Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and HNPCC-like Syndromes. http://www.hpcgg.org/LMM/comment/print/2009_HNPCC_Info_Sheet.pdf

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