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:

1. Familial Adenomatous Polyposis (FAP)
   - 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. Attenuated Familial Adenomatous Polyposis (AFAP)
     - 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.

   b. MUTYH (formerly MYH)-associated polyposis (MAP)
     - 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.

2. Lynch Syndrome (HNPCC)
Patients with Lynch syndrome have a predisposition to colorectal, and other malignancies 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 is 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 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.

In certain situations it is recommend 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 microsatellite instability (MSI) and abnormal MMR protein via immunohistochemical analysis (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 criteria:
• At-risk relatives (see Guidelines below) 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 when the following criteria is met:
• 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 (see Guidelines below) relatives of patients with Lynch syndrome with a known MMR mutation; **OR**
• 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 Policy 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.

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

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

Coverage:
Medicare excludes all screening (not just genetic screening) with certain statutory exceptions. Blue CHiP 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:
The following genetic testing of MLH1, MSH2, MSH6, PMS2 and microsatellite instability. Prior authorization is required for BlueCHiP for Medicare and recommended for all other BCBSRI products. (Effective 1/1/12):

81292
81293
81294
81295
81296
81297
81298
81299
81300
81318
81319
81301
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. (Effective 1/1/12):

**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 preauthorization is not needed:**

**Genetic Testing in Patients at Risk for Lynch Syndrome:**
83890  
83894  
83898  
83902  
83912  

**Genetic Testing in Patients at Risk for FAP**
83890  
83892  
83894  
83898  
83902  
83912  

Also known as:  
FAP  
HNPCC

**Related topics:**  
Genetic testing and counseling  
Colaris, ColarisAP  
Gene sequencing

**Published:**  
Policy Update, July 2001  
Policy Update, August 2006  
Policy Update, January 2008  
Provider Update, November 2008  
Provider Update, November 2009  
Provider Update, June 2010  
Provider Update, June 2011  
Provider Update, May 2012

**References:**


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