Medical Policy

Genetic Testing for Colorectal Cancer

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Description**

Familial adenomatous polyposis (FAP) and Lynch syndrome are two well-defined forms of hereditary colorectal cancer for which there is genetic testing available for both affected individuals and those at risk for these inherited conditions. Familial adenomatous polyposis is associated with germline mutations in the adenomatous polyposis coli (APC) gene, located on
In addition, two subset variations of FAP are attenuated FAP (aFAP) and MUTYH (formerly MYH)-associated polyposis (MAP). Attenuated FAP can be caused by a mutation of the APC gene but can also be associated with a mutation of the MUTYH gene and in that case is called MUTYH-associated polyposis (MAP). Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC) is an inherited predisposition to colorectal cancer (and other malignancies) and is associated with any of a large number of possible mutations in one of several deoxyribonucleic acid (DNA) mismatch repair (MMR) genes, known as MLH1, MSH2, MSH6, PMS2 and MLH3 or mutations or epimutations in the epithelial cell adhesion molecule (EPCAM).

Genetic testing is available for both affected individuals, as well as those at risk, for various types of hereditary cancer. This policy describes genetic testing for FAP, Lynch syndrome (formerly HNPCC), MYH-associated polyposis, and Lynch syndrome-related endometrial cancer. It is important to distinguish among these various forms of colorectal cancer by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome (Gala & Chung, 2011).

**Related Medical Policies:**
- KRAS and BRAF Mutation Analysis in Metastatic Colon Cancer
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

### Policy

**Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)**

Genetic testing for adenomatous polyposis coli (APC) gene mutations may be considered **medically necessary** for either of the following:

- At-risk relatives (See Policy Guidelines) of individuals with FAP and/or a known APC gene mutation
- Individuals with a differential diagnosis of attenuated FAP (aFAP) versus MUTYH-associated polyposis (MAP) versus Lynch syndrome.*

*Note: Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation.

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

**MUTYH (formerly MYH)-Associated Polyposis (MAP)**

Genetic testing for MUTYH gene mutations may be considered **medically necessary** when both of the following criteria are met:

- Individuals with a differential diagnosis of aFAP versus MUTYH-associated polyposis (MAP) versus Lynch syndrome
- A negative result for APC gene mutations

Note: Family history of no parents or children with FAP is consistent with MAP (autosomal recessive).
Mismatch Repair (MMR) Genes (MLH1, MSH2, MSH6, PMS2 and MLH3)

Genetic testing for mismatch repair (MMR) gene mutations may be considered medically necessary for any of the following:

- Individuals with colorectal cancer for the diagnosis of Lynch syndrome
- At-risk relatives (see Policy Guidelines) of individuals with Lynch syndrome with a known MMR mutation
- Individuals with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer (see Policy Guidelines), for the diagnosis of Lynch syndrome
- Individuals with a differential diagnosis of aFAP versus MUTYH-associated polyposis (MAP) versus Lynch syndrome (Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation)
- Individuals without colorectal cancer and both of the following:
  - A family history meeting the Amsterdam or Revised Bethesda criteria (See Policy Guidelines)
  - No affected family members have been tested for MMR mutations

Epithelial Cell Adhesion Molecule (EPCAM) Mutations

Genetic testing for epithelial cell adhesion molecule (EPCAM) mutations may be considered medically necessary when any one of the following three major criteria (solid bullets) is met:

- Individuals with colorectal cancer for the diagnosis of Lynch syndrome (see Policy Guidelines) when either of the following criteria are met:
  - Tumor tissue shows lack of MSH2 expression by immunohistochemistry and individual is negative for a germline mutation in MSH2
  - Tumor tissue shows a high level of microsatellite instability (MSI) and individual is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6
- At-risk relatives (see Policy Guidelines) of individuals with Lynch syndrome with a known EPCAM mutation
- Individuals without colorectal cancer and both of the following:
  - A family history meeting the Amsterdam or Revised Bethesda clinical criteria (See Policy Guidelines), when no affected family members have been tested for MMR mutations
  - Sequencing for MMR mutations 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 MLH1 protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

*See related Blue Shield Medical Policy: KRAS and BRAF Mutation Analysis for Metastatic Colorectal Cancer when BRAF V600E mutation analysis testing is used to predict non-response
to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

**Other Gene Mutations for Lynch Syndrome or Colorectal Cancer**

Genetic testing for all other gene mutations for Lynch syndrome or colorectal cancer is considered *investigational*.

**Genetic Counseling**

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

**Policy Guideline**

It is recommended that, when possible, initial genetic testing for FAP or Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the mutation found in the affected family member.

For individuals with colorectal cancer and a clinical presentation consistent with *classical* FAP; proband testing can provide specific codon-sequence data to target gene sequencing in at-risk relatives. However, APC gene-mutation testing in *classical* FAP patients (with hundreds to thousands of polyps), solely for the purpose of confirming the diagnosis, is generally not medically necessary.

**At-Risk Relatives:** Due to the high lifetime risk of cancer in the majority of the genetic syndromes discussed in this policy, "at-risk relatives" primarily refers to first-degree relatives (parents, siblings, and offspring). However, some judgment must be allowed, for example, in the case of a small family pedigree, when extended family members may need to be included in the testing strategy (see modified Amsterdam II clinical criteria below).

**Amsterdam II Clinical Criteria**

The Amsterdam criteria are the most stringent criteria for defining families at high risk for Lynch Syndrome.

Three or more relatives with an HNPCC-associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis) and all of the following criteria must be fulfilled:

- One should be a first-degree relative (parents, siblings, and offspring) of the other two
- Two or more successive generations affected
- One or more relatives diagnosed before the age of 50 years
- Familial adenomatous polyposis (FAP) should have been excluded in cases of colorectal carcinoma
- Tumors should be verified by pathologic examination

The modified Amsterdam II clinical criteria may be applied in either of the following situations:
• In very small families, which cannot be further expanded, with only two colorectal cancers in first-degree relatives if at least two generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years
• In families with two first-degree relatives affected by colorectal cancer and the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer

Revised Bethesda Guidelines

The Bethesda guidelines are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also felt to be more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability (MSI) and/or immunohistochemistry (IHC). The guidelines advise tumors from individuals should be tested in any of the following situations:

• Colorectal carcinoma diagnosed in a patient who is less than 50-years of age
• Presence of synchronous (at the same time) or metachronous (at another time, i.e. a recurrence of) colorectal cancer or other Lynch syndrome-associated tumors, regardless of age
• Colorectal cancer with high MSI (MSI-H) histology diagnosed in a patient less than 60-years old
• Colorectal cancer diagnosed in one or more first-degree relatives (parents, siblings, and offspring) with a Lynch syndrome-associated tumor, with one of the cancers being diagnosed at less than 50 years of age
• Colorectal cancer diagnosed in two or more first-degree (parents, siblings, and offspring) or second-degree relatives (aunts, uncles, grandparents, grandchildren, nieces, nephews, and half-siblings) with Lynch syndrome-associated tumors, regardless of age. Lynch-associated 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.

MUTYH Gene Mutations: In many cases, genetic testing for MUTYH gene mutations should first target the specific mutations Y165C and G382D, which account for more than 80% of mutations in Caucasian populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

Lynch Syndrome Screening: 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 results of 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 genetic testing is inconclusive.

MMR Gene Sequencing: When indicated, genetic sequencing for MMR gene mutations 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
mutations are expected based on IHC or MSI studies, but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

Several Clinical Laboratory Improvement Amendments (CLIA)-licensed clinical laboratories offer MMR gene mutation testing for Lynch syndrome. For example, the GeneTests website lists 18 U.S.-located laboratories that offer this service. In at least one laboratory, Lynch syndrome mutation testing is packaged under one copyrighted name (i.e., COLARIS®, Myriad Genetic Laboratories Inc, Salt Lake City, UT).

**The COLARIS® Tests**: The Colaris® tests from Myriad Genetic Laboratories Inc., (Salt Lake City, UT) include 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 may be two versions of this test, the COLARIS (excludes PMS2 testing) and COLARIS Update (includes PMS2 testing). Testing is likely done in stages, beginning with the most common types of mutations. Individualized testing (e.g., targeted testing for a family mutation) can also be requested.

**Clinical Laboratories**

GeneTests (National Center for Biotechnology Information [NCBI]), lists 15 U.S.-based CLIA-licensed clinical laboratories that provide APC mutation testing and 14 that provide MUTYH mutation testing. The COLARIS® AP test from Myriad Genetic Laboratories includes DNA sequencing analysis of the APC and MUTYH genes, as well as analysis of large rearrangements in the APC gene that are not detected by DNA sequencing.

**Genetic Counseling**: Associated genetic counseling performed by a trained genetic counselor would be coded using CPT code 96040 (Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family). Genetic counseling performed by a physician is coded using the appropriate CPT evaluation and management codes.

**Test Specific Coding:**

Genetic testing for colon cancer is not widely available and is most commonly performed by commercial reference labs or research labs dedicated to genetic testing in general. Claims for molecular genetic testing should clearly identify the test type and the indications for testing. Appropriate CPT/HCPCS codes or CPT code modifiers should be utilized when available.

**Genetic Testing of APC (FAP):**

*FAP Gene Sequencing (APC gene)* - Used for confirmation of clinical diagnosis in patients with clinical features of FAP. This test is not appropriate for asymptomatic patients with a family history of FAP. The following CPT/HCPCS codes represent testing for the APC gene:

- **81201**: APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
- **81202**: APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
- **81203**: APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
Lynch Syndrome Screening - Used for patients at high risk for Lynch Syndrome. Testing may include any or all of the following when applicable: Microsatellite instability (MSI), immunohistochemistry (IHC) testing, MLH1 and/or MSH2 gene sequencing or mutation, and/or BRAF mutation analysis and PMS2 (if applicable).

Microsatellite Instability (MSI): Used as a screening test to identify individuals eligible for germline mutation analysis of mismatch repair genes

- 81301: Microsatellite instability analysis of markers for mismatch repair deficiency, includes comparison of neoplastic and normal tissue, if performed.

BRAF Gene Mutation Analysis*

- 81210: BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant

*See related Blue Shield Medical Policy: KRAS and BRAF Mutation Analysis for Metastatic Colorectal Cancer when BRAF V600E mutation analysis testing is used to predict non-response to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

MMR Gene Mutations

MLH1 Code Range:

- 81292: MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81293: MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81294: MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

MSH2 Code Range:

- 81295: MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81296: MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81297: MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

MSH6 Code Range:

- 81298: MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81299: MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81300: MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

**PMS2 Code Range:**
- 81317: PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81218: PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81319: PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

**IHC:**
- 88342-MLH-1, Immunostain
- 88342-MSH-2, Immunostain
- 88342-MSH-6, Immunostain
- 88342-PMS-2, Immunostain

**COLARIS® Tests:**
- COLARIS® (for hereditary non-polyposis colorectal cancer) includes:
  - 81212, 81294, 81295, 81297, 81298, 81300, 81317 & 81319 (all x 1)
- COLARIS® AP (APC Analysis and MYH Mutation Panel) includes:
  - Includes PMS2: 81201 & 81203-59 modifier (all x 1)

**MUTYH Gene Analysis for Multiple Adenoma, Y165C and G382D** - Used for determining whether the clinical phenotype of multiple colorectal adenomas is due to biallelic MUTYH mutations in the affected individual or for predictive testing and familial risk assessment by carrier screening when an MUTYH mutation has been identified in an affected family member.
- 81401: Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as]:
  - MUTYH (mutY homolog [E. Coli]) (eg, MYH-associated polyposis), common variants (eg, Y165C, G382D)
- 81406: Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as]:
  - MUTYH (mutY homolog [E. coli]) (eg, MYH-associated polyposis), full gene sequence

**EPCAM Mutations:**
- 81403: Molecular pathology procedure, level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as]:

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o EPCAM (epithelial cell adhesion molecule) (eg, Lynch syndrome), duplication/deletion analysis

### Documentation Required for Clinical Review

- Referring physician's history and physical and/or consultation report(s) including:
  - Personal and/or family history of cancer (if applicable) including: family relationship, cancer site(s), age at diagnosis
  - Preliminary diagnosis and prognosis
  - Specific test(s) requested and clinical reason/justification for testing
  - Treatment plan
- Genetic counseling/professional results (if available)
- Laboratory and/or Pathology report(s) (e.g., APC gene mutations, MSH2, MMR mutations, MSI etc.)
- Laboratory invoice indicating specific test(s)/panel(s) and associated procedure codes

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.