

## Corporate Medical Policy

# Genetic Testing for Colon Cancer

**File Name:** genetic\_testing\_for\_colon\_cancer  
**Policy Number:** MED1171  
**Origination:** 5/2004  
**Last Review:** 4/2008  
**Next Review:** 4/2010

### Description of Procedure or Service

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There are currently two well-defined types of hereditary [colorectal](#) cancer, familial [polyposis](#) (FAP) and hereditary non[polyposis colorectal](#) cancer (HNPCC). FAP is typically apparent by age 10. If left untreated, all affected individuals will go on to develop [colorectal](#) cancer. FAP accounts for 1% of [colorectal](#) cancer and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina, referred to as Gardner's syndrome. Individuals with HNPCC tend to have early-onset [colorectal](#) cancer, right-sided tumors, and often multiple cancers. HNPCC is estimated to account for 3% to 5% of [colorectal](#) cancer and is also associated with an increased risk of other cancers such as [endometrial](#), ovarian, urinary tract, and [biliary](#) tract cancer. HNPCC is associated with a lifetime risk of developing [colorectal](#) cancer of approximately 80%. While FAP can be identified by the appearance of characteristic [polyps](#), the identification of HNPCC is based primarily on family history. The Amsterdam criteria are one such set of clinical criteria.

Due to concern that the Amsterdam criteria will miss many cases of HNPCC due to small family size or the occurrence of extracolonic (outside the colon) tumors, a more inclusive set of criteria, termed the Bethesda guidelines have been developed. Extracolonic cancers include [biliary](#), [endometrial](#), urinary, or ovarian cancer.

Dominantly inherited germline genetic [mutations](#) have been associated with both FAP and HNPCC. Germline [mutations](#) in the adenomatous [polyposis coli](#) (APC) gene, located on chromosome 5, are responsible for FAP. [Mutations](#) in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. In addition, a specific APC gene [mutation](#) (11307K) has been found in subjects of Ashkenazi Jewish descent that may explain a portion of the familial [colorectal](#) cancer occurring in this population. Unlike other [mutations](#) in the APC gene, which result in an alteration in the protein length, the 11307K [mutation](#) is termed a [missense mutation](#). It is hypothesized that the APC11307K [mutation](#) itself does not cause colon cancer; rather this particular [mutation](#) appears to create a weak spot in the gene that makes it more susceptible to additional genetic changes that may in turn lead to colon cancer. The presence of a specific [mutation](#) in a well-defined population creates the possibility of genetic screening of Ashkenazi Jewish individuals with or without a family history of colon cancer.

HNPCC is associated with [mutations](#) in 1 of 5 different genes, located on chromosomes 2,3, or 7. These genes are known as MLH1, MSH2, PMS1, PMS2, and MSH6; all of the genes are involved in DNA mismatch repair (MMR) mechanisms. The majority of HNPCC patients have [mutations](#) in either hMLH1 or hMSH2. As a result, sequencing for MMR gene [mutations](#) in suspected HNPCC families is usually limited to MLH1 and MSH2. The gene size and the difficulty of detecting [mutations](#) in either of these genes makes direct sequencing a time- and cost-consuming process.

Genetic testing for hereditary colon cancer may be performed in three general settings:

- In patients with colon cancer with a clinical picture or family history consistent with FAP, or with a family history suggestive of HNPCC: For the affected patient, a positive test for HNPCC [mutations](#) may

## Policy: Genetic Testing for Colon Cancer

prompt additional surveillance for emergence of an additional primary tumor of the colon or the development of extracolonic manifestation. A positive test for FAP [mutations](#) may prompt consideration of a prophylactic colectomy. A negative test is generally considered uninformative since the patient may have a mutation undetected with current methodology.

- In unaffected members of a suspected HNPCC family: A positive test in an affected family member may establish a basis for testing unaffected family members. Increased surveillance of at-risk members of HNPCC families has been shown to reduce the [colorectal](#) cancer rate due to the early detection and removal of [adenomas](#) in mutation-positive individuals. In the case of FAP, affected family members may consider a prophylactic colectomy. Members without the specific [mutations](#) have not inherited the susceptibility gene and can forego intense surveillance (although they retain the same risk as the general population and should continue an appropriate level of surveillance).
- In the diagnosis of patients with suspected Muir-Torre Syndrome: Muir-Torre Syndrome is a genetic syndrome, which is characterized by a combination of sebaceous tumors of the skin and at least one internal malignancy which is usually colon cancer. Examples of sebaceous skin neoplasia are sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, and keratoacanthoma.

Various attempts have been made to identify which patients with colon cancer should undergo testing for HNPCC [mutations](#). 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. For example, patients younger than 45 years old who have colon cancer meet the Bethesda guidelines. The Bethesda guidelines are the most sensitive clinical criteria for identification of HNPCC patients (approximately 94%), but are least specific (approximately 25%); thus, additional indirect screening methods are needed to determine which patients should proceed to direct testing for MMR gene [mutations](#).

[Mutations](#) in MMR genes result in a failure of the mismatch repair system to repair errors that occur during the replication of DNA in tumor tissue. Such errors are characterized by the accumulation of alterations (due to insertions or deletions) in the length of simple, repetitive microsatellite (2 to 5 base repeats) sequences that are distributed throughout the genome. In HNPCC, one MMR gene [mutation](#) is inherited; errors in microsatellite sequences follow somatic activation of the other MMR gene allele in precancerous and cancerous cells. Thus, detection of alterations in microsatellite sequences (termed microsatellite instability or MSI) reflects a biological consequence of malignancy, rather than just an associated marker.

In an attempt to standardize the approach to MSI testing, a panel of 5 microsatellite markers has been recommended as a reference for detecting sites of MSI and an accompanying list of alternate markers has been published subsequent to a National Cancer Institute (NCI) workshop; other published marker panels have been shown to perform similarly. Tumor tissue may be molecularly characterized as having high-frequency microsatellite instability (MSI-H) if at least 30%-40% of test markers (at least 5) show instability when compared to matched normal tissue. When only 1 of 5 markers shows instability, some recommend further testing with additional markers.

The Bethesda guidelines were developed to assist in the selection of patients whose tumors should be analyzed for MSI and to identify patients with possible HNPCC. Because patients with the MSI-H tumors have been missed because of older age at diagnosis only, less stringency with regard to "age at disease onset" may be appropriate. MSI-H is found in 95% of HNPCC cancers and in a high proportion of [polyps](#) from HNPCC patients. However, the specificity of MSI-H is low because 10%-15% of sporadic [colorectal](#) cancers without HNPCC demonstrate MSI-H; thus, the presence of MSI-H does not confirm HNPCC. Patients with cancer who test positive for MSI-H are then tested for [mutations](#) in MMR genes, usually limited to MLH1 and MSH2. Using family history followed by MSI analysis on eligible individuals to screen all newly diagnosed [colorectal](#) cancer has been shown in one study to be cost-effective at \$7,557 per year of life gained when patients and at-risk family members are considered together.

Absent or reduced protein expression may be a consequence of an MMR gene [mutation](#). Immunohistochemistry (IHC) assays for the expression of MLH1 and MSH2 can be used to detect loss of expression of

## Policy: Genetic Testing for Colon Cancer

these genes and to focus HNPCC [mutation](#) testing efforts on a single gene. It is also possible for IHC assays to show loss of expression, and thus indicate the presence of a [mutation](#), when HNPCC [mutation](#) testing is negative for a [mutation](#). In such cases, [mutations](#) may be in regulatory elements that cannot be detected. IHC technology is readily available in many clinical laboratories; it may be possible to substitute IHC screening for MSI screening. However, a result of MSI-H and no loss of MLH1 or MSH2 expression by IHC could also indicate a rare [mutation](#) in a different MMR gene. Thus, although the results of MSI and IHC testing are usually overlapping, in some cases they may provide complimentary information.

Recently, there has been interest in evaluating MSI from shed [colorectal](#) cancer cells isolated from stool samples. This is referred to in this policy as DNA analysis of stool samples. Two general populations of patients have been studied:

1. Known or suspected carriers of HNPCC [mutation](#), considered at high risk of developing [colorectal](#) cancer. In this setting, testing of fecal samples for MSI may be used to monitor patients form development of [colorectal](#) cancer. The test may be used either in lieu of routinely scheduled surveillance colonoscopies, or during intervals between scheduled colonoscopies. Those patients testing positive for MSI may be further evaluated with colonoscopy.
2. In patients at average risk of [colorectal](#) cancer. In this setting, testing of fecal samples for MSI may be offered in lieu of, or as an adjunct to, other recommended [colorectal](#) cancer screening test, including fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, or double contrast barium enema.

Exact Sciences (Maynard, MA) has developed fecal testing for MSI. The PreGen-26™ test, offered through reference laboratories, is designed to detect deletions in BAT-26, a single nucleotide tract consisting of 26 adenosines. BAT-26 is thought to be the best marker for detecting microsatellite instability. The PreGen Plus is designed to detect 20 different [mutations](#) in genes for p53, BAT-26, and K-Ras. K-Ras is an oncogene whose activity may be increased by [mutations](#); TP 53 is a tumor suppressor gene whose activity may be decreased by [mutations](#); and BAT-26 is used as a marker for MSI, as described above. These genetic changes are thought to be associated with the stepwise neoplastic transformation of normal [colorectal](#) mucosa to benign [adenomas](#) to malignant adenocarcinomas. In addition, the PreGen-Plus test is designed to detect "long" DNA (longer than 200 base pairs), i.e., high molecular weight DNA, which is associated with non-apoptotic colonocytes that are typically shed from neoplasms. In contrast, cells shed from normal [colorectal](#) mucosa are typically cleaved into short fragment lengths of less than 200 base pairs.

The American Cancer Society and the American Gastroenterological Association do not recommend analysis of human DNA in stool samples for [colorectal](#) screening. The American Cancer Society's Colorectal Cancer Advisory Group concluded that there is insufficient evidence to determine whether fecal DNA testing can be recommended for average-risk individuals.

**Note: The clinical indications and discussion of Genetic Testing for Colon Cancer is complex and technical. If you have any questions concerning this treatment, please talk with your physician.**

## Policy

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BCBSNC will provide coverage for Genetic Testing for Colon Cancer when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

BCBSNC **will not** provide coverage for DNA Analysis in Stool Samples because it is considered investigational as a screening technique for colorectal cancer. BCBSNC does **not** cover investigational procedures.

## Policy: Genetic Testing for Colon Cancer

### Benefits Application

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Please refer to Certificate for availability of benefits. This policy relates only to the services or supplies described herein. Benefits may vary according to benefit design, therefore certificate language should be reviewed before applying the terms of the policy.

Please review Certificate for availability and limitations regarding benefits for genetic testing and counseling.

### When Genetic Testing for Colon Cancer is covered

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- A. **Adenosis Polyposis Coli (APC)** Genetic testing to determine carrier status of the adenosis **polyposis** coli gene (APC) may be considered medically necessary in the following subjects:
1. patients with greater than 20 colonic **polyps**; OR
  2. in first-degree relatives (i.e., siblings, parents, offspring) of patients diagnosed with familial adenomatous **polyposis** (FAP) with a known genetic **mutation**.
- B. **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)** Genetic testing to determine the carrier status of the HNPCC gene may be considered medically necessary in patients with colorectal cancer who meet either the Amsterdam or Bethesda Criteria as described below:
1. **Amsterdam II criteria** (patients must meet **ALL** of the following):
    - a. Three or more relatives with a histologically verified colorectal cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two; **AND**
    - b. HNPCC-associated cancer involving at least two generations; **AND**
    - c. Cancers in 1 or more affected relatives diagnosed before 50 years of age; **AND**
    - d. Familial adenomatous polyposis excluded in any cases of colorectal cancer.Modifications allow for small HNPCC families: these families must have 2 colorectal cancers in first-degree relatives involving at least 2 generations, with at least 1 individual diagnosed by age 55.
  2. Revised **Bethesda Criteria** (patients may meet **ANY** of the following):
    - a. Individuals diagnosed with colorectal cancer before age 50; **OR**
    - b. Individuals with HNPCC-related cancer, including synchronous and metachronous colorectal cancers or associated extracolonic cancers; **OR**
    - c. Individuals with colorectal cancer with the MSI-H histology diagnosed in a patient less than age 60; **OR**
    - d. Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and /or a colorectal **adenoma**; one of the cancers diagnosed at age <50 years; **OR**
    - e. Individuals with colorectal cancer and colorectal cancer diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors regardless of age; OR
- C. Genetic testing to determine the carrier status of the HNPCC gene may be considered medically necessary in patients without a history of colorectal cancer but who have a first- or second-degree relative with a known HNPCC **mutation**.

## Policy: Genetic Testing for Colon Cancer

- D. **The microsatellite instability (MSI) test and the immunohistochemistry (IHC) test** of expression of MLH1 and MSH2, may be considered medically necessary as a means of identifying which patients with colon cancer, who also meet Amsterdam or Bethesda criteria, should undergo HNPCC genetic testing. MSI and IHC testing may also provide some additional information when HNPCC genetic testing is inconclusive
- E. **The microsatellite instability (MSI) test and the immunohistochemistry (IHC) test** of expression of MLH1 and MSH2, may be considered medically necessary as a means of identifying patients with Muir-Torre Syndrome which may be associated with HNPCC.
- F. **DNA Analysis in Stool Samples as a technique to screen for colorectal cancer** is **not** covered, see below.
- G. **Pre- and post-genetic counseling** may be considered medically necessary as an adjunct to the genetic testing itself.

### When Genetic Testing for Colon Cancer is not covered

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Genetic testing for colon cancer is not covered under the following conditions:

- A. When the criteria listed above has not been met.
- B. DNA analysis of stool samples as a technique to screen for colorectal cancer is considered **investigational** as a screening technique for colorectal cancer in both patients with average to moderate risk, and in patients considered at high risk for colorectal cancer.

### Policy Guidelines

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The American Cancer Society Colorectal Cancer (ACS CRC) Advisory Committee and the U.S. Preventive Services Task Force (USPSTF) plan to update their guidelines in the near future, and evaluation of the evidence for fecal DNA screening will be considered in their review. Currently there is insufficient evidence to determine if this test can be recommended for colorectal screening. Additional studies are needed to determine the best markers for DNA detection of colon cancer. DNA testing of stool samples is less sensitive than colonoscopy which is considered the standard of care. Final test configuration of DNA analysis of stool and its performance in an unselected, average-risk screening population continue to need evaluation for use in colorectal screening programs.

### Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 83890, 83892, 83894, 83896, 83898, 83902, 83903, 83904, 83905, 83906, 83912, S3828, S3829, S3830, S3831, S3833, S3834, S3890.*

There is no specific CPT code for genetic testing; testing is typically coded for using a series of CPT codes describing the individual steps in the testing process.

HCPCS codes listed above are more specific to the genetic tests provided, and should be used when appropriate.

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.

There is no specific CPT code for associate genetic counseling, which is typically performed by a medical

## Policy: Genetic Testing for Colon Cancer

oncologist or medical geneticist, or a psychotherapist. CPT codes for an office visit may be used.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

### Policy Key Words

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Key Words: genetic testing for inherited susceptibility to colon cancer including microsatellite instability, cancer, Fecal Testing, MSI, Pre-Gen-26, HNPCC, FAP, Familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, BAT-26, Pre-Gen Plus, K-Ras, DNA fecal analysis, stool analysis, Muir-Torre Syndrome, MD1171

### Medical Term Definitions

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#### **Adenoma**

a benign tumor of a glandular structure.

#### **Biliary**

pertaining to the bile, to the bile ducts, or to the gallbladder.

#### **Colorectal**

pertaining to the colon and rectum.

#### **Endometrial**

lining of the uterus.

#### **Missense**

relating to or being a genetic mutation.

#### **Mutation**

a change in genetic material.

#### **Polyp**

a benign growth protruding from a mucous membrane.

#### **Polyposis**

the presence of many polyps

### Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.08, 12/17/03.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.29, 10/9/03.

ECRI. (2002, January) Microsatellite instability testing for hereditary nonpolyposis colorectal cancer (Issue No. 64) Windows on Medical Technology.

## Policy: Genetic Testing for Colon Cancer

Specialty Matched Consultant Advisory Panel - 5/2004

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.29, 4/1/2005.

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American Cancer Society. (2005). Cancer reference information. colorectal cancer: early detection.

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[CRI\\_2\\_6X\\_Colorectal\\_Cancer\\_Early\\_Detection\\_10.asp](http://www.cancer.org/docroot/CRI/content/CRI_2_6X_Colorectal_Cancer_Early_Detection_10.asp)

Specialty Matched Consultant Advisory Panel - 4/2006

Specialty Matched Consultant Review 5/18/2007

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.29, 9/18/07.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.08, 4/25/06.

Specialty Matched Consultant Advisory Panel - 4/2008

### Policy Implementation/Update Information

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- 6/10/04 New policy originated. Genetic Testing for Colon Cancer may be covered when medically necessary criteria is met. Specialty Matched Consultant Advisory Panel review. Notification 6/10/2004. Effective date 8/12/2004.
- 1/5/06 No change in policy statement. References added.
- 5/22/06 Specialty Matched Consultant Advisory Panel review 4/20/2006. Updated the Amsterdam II and Revised Bethesda Criteria in the "When Covered" section. Added HCPCS codes S3828, S3829, S3830, S3831, S3833, S3834, S3890 as they relate to this policy. References added.
- 8/13/07 Added information related to Muir-Torre Syndrome to "Description" section. Added the following to the "When Covered" section; "E. The microsatellite instability (MSI) test and the immunohistochemistry (IHC) test of expression of MLH1 and MSH2, may be considered medically necessary as a means of identifying patients with Muir-Torre Syndrome which may be associated with HNPCC.". References added.
- 6/16/08 Specialty Matched Consultant Advisory Panel review 4/30/08. No change to policy statement. Rationale updated in "Policy Guidelines" section. References added.

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.