

Policy terminated because S codes in the policy have not been covered since July 2011 and there is no current Medicaid policy.

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1.0 Description of the Procedure, Product, or Service

There are currently two well-defined types of hereditary colorectal cancer, familial polyposis (FAP) and hereditary nonpolyposis 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:

- a. In recipients with colon cancer with a clinical picture or family history consistent with FAP, or with a family history suggestive of HNPCC: For the affected recipient, a positive test for HNPCC mutations may 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 recipient may have a mutation undetected with current methodology.
- b. In unaffected recipients 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 recipients of HNPCC families has been shown to reduce the colorectal cancer rate due to the early detection and removal of adenomas in mutation-positive recipients. 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).
- c. In the diagnosis of recipients 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 recipients 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, recipients 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 recipients (approximately 94%), but are least specific (approximately 25%); thus, additional indirect screening methods are needed to determine which recipients 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 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:

- a. 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.
- b. 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.

1.1 Medical Term Definitions

- a. Adenoma: a benign tumor of a glandular structure.
- b. Biliary: pertaining to the bile, to the bile ducts, or to the gallbladder.
- c. Colorectal: pertaining to the colon and rectum.
- d. Endometrial: lining of the uterus.
- e. Missense: relating to or being a genetic mutation.
- f. Mutation: a change in genetic material.
- g. Polyp: a benign growth protruding from a mucous membrane.
- h. Polyposis: the presence of many polyps.

2.0 Eligible Recipients

2.1 General Provisions

To be eligible, NCHC recipients must be enrolled on the date of service.

3.0 When the Procedure, Product, or Service Is Covered

3.1 General Criteria

NCHC covers procedures, products, and services related to this policy when they are medically necessary and

- a. the procedure, product, or service is individualized, specific, and consistent with symptoms or confirmed diagnosis of the illness or injury under treatment, and not in excess of the recipient's needs;
- b. the procedure, product, or service can be safely furnished, and no equally effective and more conservative or less costly treatment is available; **AND**
- c. the procedure, product, or service is furnished in a manner not primarily intended for the convenience of the recipient, the recipient's caretaker, or the provider.

3.2 Specific Criteria

Genetic Testing for Colon Cancer is covered under the NC Health Choice Program when it is determined to be medically necessary because the following medical criteria have been met:

- 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. recipients with greater than 20 colonic polyps; **OR**

2. in first-degree relatives (i.e., siblings, parents, offspring) of recipients 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 recipients with colorectal cancer who meet either the Amsterdam or Bethesda Criteria as described below:
 1. Amsterdam II criteria (recipients 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;
 - (b) HNPCC-associated cancer involving at least two generations;
 - (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 - recipients may meet ANY of the following:
 - (a) Recipients diagnosed with colorectal cancer before age 50;
 - (b) Recipients with HNPCC-related cancer, including synchronous and metachronous colorectal cancers or associated extracolonic cancers;
 - (c) Recipients with colorectal cancer with the MSI-H histology diagnosed in a recipient less than age 60;
 - (d) Recipients 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;
 - (e) Recipients 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 recipients without a history of colorectal cancer but who have a first- or second-degree relative with a known HNPCC mutation.
- 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 recipients 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 recipients with Muir-Torre Syndrome which may be associated with HNPCC.

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

4.0 When the Procedure, Product, or Service Is Not Covered

4.1 General Criteria

Procedures, products, and services related to this policy are not covered when

- a. the recipient does not meet the eligibility requirements listed in **Section 2.0**;
- b. the recipient does not meet the medical necessity criteria listed in **Section 3.0**;
- c. the procedure, product, or service unnecessarily duplicates another provider's procedure, product, or service; or
- d. the procedure, product, or service is experimental or investigational.

4.2 Specific Criteria

Genetic testing for colon cancer is not covered in the following situations:

- a. When the criteria listed in **Subsection 3.2** have 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 recipients with average to moderate risk, and in recipients considered at high risk for colorectal cancer.

4.3 Medical Policy Guidelines

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.

5.0 Requirements for and Limitations on Coverage

5.1 Prior Approval

Prior approval is not required for genetic testing for colon cancer.

6.0 Providers Eligible to Bill for the Procedure, Product, or Service

To be eligible to bill for procedures, products, and services related to this policy, providers shall

- a. meet NCHC qualifications for participation;
- b. be currently enrolled with NCHC; **AND**
- c. bill only for procedures, products, and services that are within the scope of their clinical practice, as defined by the appropriate licensing entity.

7.0 Additional Requirements

7.1 Compliance

Providers must comply with all applicable federal, state, and local laws and regulations, including o the Health Insurance Portability and Accountability Act (HIPAA) and record retention requirements.

8.0 Policy Implementation/Revision Information

Original Effective Date: July 1 2010

Revision Information:

Date	Section Revised	Change
July 1 2010	Throughout	Policy Conversion: Implementation of Session Law 2009-451, Section 10.32 “NC HEALTH CHOICE/PROCEDURES FOR CHANGING MEDICAL POLICY.”
4/30/12	Throughout	Policy Termination

Attachment A: Claims-Related Information

Reimbursement requires compliance with all NCHC guidelines.

A. Claim Type

Professional (CMS-1500/837P transaction)

B. Diagnosis Codes

Providers must bill the ICD-9-CM diagnosis codes(s) to the highest level of specificity that supports medical necessity.

C. Procedure Code(s)

CPT Codes				
83890	83892	83894	83896	83898
83902	83903	83904	83905	83906
83912				

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

D. Modifiers

Providers are required to follow applicable modifier guidelines.

E. Billing Units

The appropriate procedure code(s) used determines the billing unit(s).

F. Place of Service

Outpatient Hospital and Office

G. Co-payments

Co-payment(s) may apply to covered prescription drugs and services.

H. Reimbursement

Providers must bill their usual and customary charges.

Date of Termination: 04.30.2012