

Corporate Medical Policy

Genetic Testing for Colon Cancer

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Last Review: 11/2011

Description of Procedure or Service

There are currently two well-defined types of hereditary colorectal cancer, familial polyposis (FAP) and Lynch Syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC).

Genetic testing is available for both affected individuals, as well as those at risk, for various types of hereditary colon cancer. This policy describes genetic testing for familial adenomatous polyposis (FAP), Lynch Syndrome (formerly known as HNPCC), as well as MYH-associated polyposis.

Familial adenomatous polyposis

FAP typically develops by age 16 and can be identified by the appearance of hundreds to thousands of characteristic precancerous colon polyps. 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. These collective extraintestinal manifestations of FAP are sometimes referred to as Gardner syndrome. FAP may also be associated with CNS tumors, referred to as Turcot syndrome.

Germline mutations in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Mutations in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. 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.

A subset of FAP patients may have attenuated FAP (AFAP), characterized by 10-99 cumulative colorectal adenomas occurring later in life than in classical FAP, colorectal cancer occurring at an average age of 50-55 years, fewer extraintestinal cancers, but a high lifetime risk of colorectal cancer of about 70% by age 80. Only 30% or fewer of AFAP patients have APC mutations; some of these patients instead have mutations in the MYH gene and are then diagnosed with MYH-associated polyposis (MAP). MAP occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. Biallelic MYH mutations are associated with a cumulative colorectal cancer risk of about 80% by age 70, whereas monoallelic MYH mutation-associated risk of colorectal cancer appears to be relatively minimal. Thus, inheritance for high-risk colorectal cancer predisposition is autosomal recessive in contrast to FAP. 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, MYH if APC is negative for mutations, and screening for mutations associated with Lynch syndrome.

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Lynch syndrome

Lynch syndrome is estimated to account for 2% to 4% of colorectal cancer and is also associated with an increased risk of other cancers such as endometrial, ovarian, urinary tract, and biliary tract cancer. Lynch syndrome is associated with a risk of developing colorectal cancer of approximately 15% by age 40 and 40% by age 70, although these estimates vary considerable among studies. Lynch syndrome patients who have colorectal cancer also have an estimated 16% risk of a second primary within 10 years.

Patients with Lynch syndrome have a predisposition to colorectal cancer and other malignancies as a result of an inherited mutation in a DNA mismatch repair (MMR) gene. The term “HNPCC” originated prior to the discovery of explanatory MMR mutations for many of these patients, and now includes some who are negative for MMR mutations and likely have mutations in as-yet unidentified genes. For purposes of clarity and analysis, the use of Lynch syndrome in place of HNPCC has been recommended. 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.

Analysis of human DNA in stool samples as a technique for colorectal cancer screening

Tumor-associated gene mutations and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Since cancer cells are shed into stool, tests have been developed that detect these genetic alterations in the DNA from shed colorectal cancer cells isolated from stool samples. This has been proposed for use in screening two populations of patients for colon cancer

- 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 over time for development of colorectal cancer. The test could be used either in lieu of routinely scheduled surveillance colonoscopies or during intervals between scheduled colonoscopies. Those patients testing positive for cancer-related genetic alterations could be further evaluated with colonoscopy.
- 2.) In patients at average risk of colorectal cancer. In this setting, testing of fecal samples could be offered in lieu of, or as an adjunct to, other recommended colorectal cancer screening tests, including fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, or double contrast barium enema.

Several types of tests have been evaluated in studies and some have been marketed. One of these, PreGen-Plus™, is subject to U.S. Food and Drug Administration (FDA) regulation as a medical device, and has not been cleared by the FDA. As a consequence, and as a result of studies showing better performance of other tests, this test is no longer offered.

The currently available test is called ColoSure™, developed by OncoMethylome, which detects aberrant methylation of the vimentin (hV) gene. This test is offered as a laboratory-developed test, not subject to FDA regulation.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

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.

Analysis of Human DNA in Stool Samples is considered investigational as a screening technique for colorectal cancer. BCBSNC does not provide coverage for investigational services and procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's

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Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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

When genetic testing for colon cancer is covered

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

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

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

- Patients with a differential diagnosis of attenuated FAP vs. MYH-associated polyposis vs. Lynch syndrome and a negative result for APC gene mutations. Family history of no parents or children with FAP is consistent with MYH-associated polyposis (autosomal recessive).

Genetic testing for **MMR** gene mutations is considered **medically necessary** in the following patients:

- Patients with colorectal cancer, for the diagnosis of Lynch syndrome.
- At-risk relatives (see Policy Guidelines) of patients with Lynch syndrome with a known MMR mutation.
- Patients with a differential diagnosis of attenuated FAP vs. MYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation.
- 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.

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

When genetic testing for colon cancer is not covered

Genetic testing for colon cancer is not covered when the criteria listed above have not been met.

Genetic testing for APC gene mutations is not medically necessary for colorectal cancer patients with classical FAP.

DNA analysis of stool samples is considered **investigational** as a screening technique for colorectal cancer in patients with average, moderate, or high risk for colorectal cancer.

Policy Guidelines

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. Due to the high lifetime risk of cancer of the majority of the genetic syndromes discussed in this policy, "at-risk relatives" primarily refers to first-degree relatives. 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.

Specific contract language must be reviewed and considered when determining coverage for testing. In some cases, coverage for testing the index case may be available through the health plan benefits that

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cover the unaffected individual who will benefit from knowing the results of genetic test.

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.

No clinical trials have been published that evaluate use of DNA stool tests in those at high risk for colon cancer. The U.S. Preventive Services Task Force updated their guidelines for colon cancer screening in 2008, where fecal DNA testing was judged to have insufficient evidence to assess the benefits and harms of testing for all populations.

Billing/Coding/Physician Documentation Information

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. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81317, 81318, 81319, 83890, 83891, 83892, 83894, 83896, 83898, 83902, 83903, 83904, 83905, 83906, 83907, 83912, 96040, 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.

There are CPT genetic testing modifiers specific to MLH1 (-OJ), and MSH2, MSH6 or PMS2 (-OK).

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.

Associated genetic counseling performed by a trained genetic counselor would be coded using CPT 96040. Genetic counseling performed by a physician is coded using the appropriate evaluation and management codes.

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.

Scientific Background and Reference Sources

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.

Specialty Matched Consultant Advisory Panel - 5/2004

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

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.08, 5/23/2005.

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

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Retrieved 10/10/2005 from 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

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.29, 12/10/09

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.08, 2/11/10

Specialty Matched Consultant Advisory Panel – 10/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.29, 11/10/11

Policy Implementation/Update Information

- 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.(btw)
- 6/22/10 Policy Number(s) removed (amw)
- 11/23/10 Description section revised. When Covered section reformatted, intent of policy is unchanged. Added codes 89891, 83907 and 96040 to the Billing/Coding section. Specialty Matched Consultant Advisory Panel review 10/28/10. (adn)
- 11/8/11 Extensive revisions to Description section and Policy Guidelines section. No change in medical coverage criteria. Specialty Matched Consultant Advisory Panel review 10/26/11. (adn)
- 1/1/12 Added the following 2012 CPT codes to the "Billing/Coding" section: 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81315, 81316, 81317, 81318, and 81319. (btw)
- 1/24/12 Removed 81315 and 81316 from Billing/Coding section as they do not apply to this policy. Reference added. (btw)
- 3/30/12 Deleted HCPCS codes S3828, S3829, S3830, and S3831 from Billing/Coding section. (btw)

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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.