



CIGNA HEALTHCARE COVERAGE POSITION

Subject Genetic Testing for Susceptibility to Colorectal Cancer

Revised Date 1/15/2005
Original Effective Date 3/15/2004
Coverage Position Number 0014

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Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. ©2005 CIGNA Health Corporation

Coverage Position

CIGNA HealthCare covers genetic testing for susceptibility to colorectal cancer, including pre- and post-test genetic counseling, when ALL of the following medical necessity criteria are met:

- **Familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP) genetic testing** (i.e., testing for mutations in the adenomatous polyposis coli gene) is covered for **ANY** of the following reasons:
 - to confirm the diagnosis of FAP in patients with a personal history of suspected FAP (≥ 100 colorectal adenomas)
 - to confirm the diagnosis in patients with a personal history of suspected AFAP (≥ 20 cumulative colorectal adenomas)
 - presymptomatic testing for first-degree[†] relatives (age 10 or older) of patients with diagnosis of FAP
 - presymptomatic testing for first-degree[†] relatives (age 10 or older) of patients with diagnosis of AFAP

- **Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch Syndrome** genetic testing in affected patients (i.e., patients with colorectal cancer) is covered when either the Amsterdam II Criteria **OR** the Bethesda Guidelines are met. Criteria and Guidelines are as follows:
 - **Amsterdam II Criteria (the patient must meet ALL of the following criteria):**
 - three or more relatives with histologically verified HNPCC-associated cancer (colorectal, endometrial, small bowel, stomach, ovary, ureter and renal pelvis, brain, hepatobiliary tract, or skin [sebaceous tumors]), one of whom is a first-degree[†] relative of the other two
 - involving at least two successive generations

- one or more cancer cases diagnosed before age 50
 - familial adenomatous polyposis (FAP) excluded as a diagnosis
- **Revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI) 2004.** Tumors from individuals should be tested for microsatellite instability in the following situations, and the patient must meet **ANY ONE** of the following criteria:
- colorectal cancer diagnosed under age 50
 - presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age
 - colorectal cancer with the MSI-H histology diagnosed in a patient who is under age 60
 - colorectal cancer diagnosed with one or more first-degree[†] relatives with an HNPCC-related tumor, with one of the cancers diagnosed under age 50
 - colorectal cancer diagnosed in two or more first- or second-degree[†] relatives with an HNPCC-related tumor, regardless of age
- **Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch Syndrome** genetic testing is covered in an **unaffected patient** who has a first- or second-degree[†] relative with a known HNPCC mutation.
 - **Microsatellite instability (MSI) tumor sample testing** is covered as an initial screen in affected colorectal cancer patients who meet the Bethesda Guidelines, in order to identify those patients who should proceed with HNPCC mutation analysis.

† A **first-degree** relative is defined as a blood relative with whom an individual shares approximately 50% of their genes, including the individual's parents, full siblings, and children.

A **second-degree** relative is defined as a blood relative with whom an individual shares approximately 25% of their genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

Note: All participants undergoing genetic testing for susceptibility to colorectal cancer should have both pre- and post-test genetic counseling with a licensed or certified genetic counselor or physician, trained specifically in cancer genetics.

CIGNA HealthCare does NOT cover genetic testing for susceptibility to colorectal cancer for the following because it is considered not medically necessary or of unproven benefit (this list may not be all-inclusive):

- genetic screening for susceptibility to FAP or HNPCC in the general population
- testing of patients under age 18 for HNPCC, as this population has not been well-studied
- genetic testing for the APC1307K missense mutation
- immunohistochemistry (IHC) testing of MLH1 or MSH2 expression to prescreen patients for further HNPCC mutation analysis

General Background

Colorectal cancer is considered the third most frequently diagnosed cancer in the United States in both men and women. It is also the second leading cause of cancer death after lung cancer. In the general population, the lifetime risk of colorectal cancer is approximately 5-6%. It has been estimated that, while 75-80% of patients with colorectal cancer have sporadic disease, the remaining 20-25% have an inherited susceptibility to the disease.

The etiology of colorectal cancer is heterogeneous and may be influenced by both the environment and genetics. In general, colorectal cancer evolves in an adenoma-to-carcinoma sequence during which a

series of somatic alterations accumulate in the deoxyribonucleic acid (DNA) of the tumor tissue (ACMG/ASHG, 2000).

Mutations on several genes are associated with hereditary colorectal cancer. The adenomatous polyposis coli (APC) gene has been linked to familial adenomatous polyposis (FAP), while DNA mismatch repair genes (i.e., MSH2, MLH1, PMS1, PMS2, MSH3, and MSH6) appear connected to hereditary nonpolyposis colorectal cancer (HNPCC).

Familial Adenomatous Polyposis (FAP) and Attenuated Familial Adenomatous Polyposis (AFAP)

Familial adenomatous polyposis is an autosomal-dominant condition (i.e., each offspring of a person with FAP has a 50% chance of inheriting the gene for the disease) that is associated with mutations of the APC gene. It is characterized by a young onset (age 12-15 years) and the development of multiple (at least 100) adenomatous polyps in the colon and rectum. Patients with FAP are also at increased risk for gastric polyps, duodenal cancer, thyroid cancer, hepatoblastoma, cutaneous lesions, pancreatic cancer, brain cancer, and desmoid tumors. Considered almost 100% penetrant, adenomas develop in approximately half of all patients with FAP by age 15, and in 95% by age 35. Without intervention, most individuals with FAP will develop colon or rectal cancer by the fourth decade of life. Thus, screening and intervention for at-risk persons is critical and typically begins at puberty.

AFAP, an attenuated variety of FAP, is characterized by fewer than 100 adenomatous polyps (synchronous and metachronous) in the colorectum with proximal predominance and later onset (age 55) (ACMG/ASHG, 2000). Mutations of the APC gene are also associated with AFAP.

Most cases of FAP and AFAP are associated with mutations in the adenomatous polyposis coli (APC) gene, a tumor suppressor or gatekeeper gene that controls cell proliferation. More than 300 different disease-associated mutations of the APC gene have been identified. Most are insertions, deletions and nonsense mutations that lead to frame shifts or premature stop codons, resulting in truncation of the APC gene product.

A missense mutation of the APC gene known as APC11307K has recently been discovered as a cause of an undefined proportion of familial colorectal cancer in a specific ethnic group (American Gastroenterological Association [AGA], 2001). This mutation is associated with increased risk of colorectal adenoma and carcinoma; however, the risk is not as high as in FAP. The variant, which has been found to occur only in the Ashkenazi Jewish population, with a prevalence of 6%, is found in 10% of colorectal cancer patients who are of Ashkenazi Jewish heritage and in up to 28% of such patients who also have a positive family history of colon cancer (American College of Medical Genetics [ACMG]/American Society of Human Genetics [ASHG], 2000). The APC11307K mutation does not in itself cause polyposis or cancer, but rather creates a small, hypermutable region of the gene, indirectly causing cancer predisposition (National Cancer Institute [NCI], 2003). While genetic testing for this mutation is possible, the clinical utility of testing has not been established. According to the NCI, "no screening outcomes have been assessed in carriers of I1307K. Therefore it is not yet known whether the I1307K carrier state should guide decisions about the age at which screening is initiated, the optimal screening strategy, or the optimal screening interval" (NCI, 2003).

Summary of Evidence for FAP/AFAP Genetic Testing

The greatest utility in being able to identify an individual as having an increased risk of colorectal cancer due to a genetic mutation would be to prevent the development of cancer or to reduce cancer-related morbidity or mortality once cancer has developed. The literature contains clear evidence demonstrating that identifying carriers of the APC genetic mutations affects health outcomes positively. Clinical benefits include the ability to target surveillance methods, to estimate cancer risk more accurately, and to target treatment options for colorectal cancer prevention.

Evidence in the published, peer-reviewed scientific literature indicates that genetic testing for mutations in the APC gene is appropriate for a specific subset of individuals who have been identified as at high risk for FAP or AFAP. Among the specialty organizations that have recognized the role of FAP and AFAP genetic testing are the American Gastroenterological Association, the American College of Medical Genetics, the National Comprehensive Cancer Network and the National Cancer Institute. It is generally accepted that genetic testing for FAP and AFAP is appropriate:

- to confirm the diagnosis of FAP in an affected patient
- to provide presymptomatic testing for at-risk relatives (usually first-degree) of FAP-affected patients
- to confirm the diagnosis of attenuated FAP in individuals with at least 20 adenomas
- to provide presymptomatic testing for first-degree relatives of attenuated FAP patients

Management/Treatment Strategies for Patients with Known FAP Mutations

- **Increased surveillance** (screening begins earlier in life and with shorter intervals between screenings than general population):
 - annual physical examination
 - annual flexible sigmoidoscopic surveillance to monitor for polyps at an early age (i.e., age 10-15 years)
 - as hepatoblastoma occurs in about one in 300 patients at risk for FAP under age five, screening of alpha-fetoprotein levels and imaging of the liver of children of parents affected with FAP from infancy to age five may be recommended (AGA, 2001)
 - baseline upper endoscopy at age 25-30
- **Surgery:** If polyposis has manifested itself, the only effective management is colectomy or subtotal colectomy (the timing of the surgery and the particular procedure performed will vary depending on individual circumstances, such as the patient's age).
- **Chemoprevention:** Some experts recommend chemoprevention with non-steroidal anti-inflammatories (NSAIDS) to reduce polyp burden.

Management/Treatment Strategies for Patients with Known AFAP Mutations

- **Increased surveillance** (screening begins earlier in life and with shorter intervals between screenings than general population):
 - annual physical examination
 - annual or biennial colonoscopy (rather than flexible sigmoidoscopy, as the adenoma can be predominantly right-sided)
 - baseline upper endoscopy beginning at age 25-30
- **Surgery:** Colonoscopy with polypectomy or colectomy with ileorectal anastomosis is recommended, depending on adenoma burden.
- **Chemoprevention:** Some experts recommend chemoprevention with NSAIDS to reduce polyp burden.

Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is the most common type of hereditary colorectal cancer, accounting for 20-35% of all inherited forms. HNPCC is characterized by the familial aggregation of a spectrum of cancer arising at an early age (approximately age 45) (NCCN, 2003), with a predominance of right-sided colorectal cancer. Unlike FAP, the colorectal cancer in HNPCC arises from a single colorectal lesion in the absence of polyposis (AGA, 2001). HNPCC is also associated with an increased risk of extracolonic cancers, the most common being endometrial cancer. Other associated extracolonic cancers include ovarian, stomach, small bowel, pancreatic, hepatobiliary, brain and ureteral cancers.

HNPCC is an autosomal-dominant condition that results from mutations in mismatch repair genes (MSH2, MLH1, PMS1, PMS2, MSH3 and MSH6). HNPCC accounts for 2-5% of all colorectal cancer cases and is associated with a lifetime risk of colon or rectal cancer approaching 80%. These mismatch repair genes

are classified as "caretaker genes," because their function is to maintain the "fidelity" of DNA during replication. The MSH2 and MLH1 genes are thought to account for the majority of the mutations.

Microsatellite Instability

Microsatellite instability (MSI) is found in the colorectal cancer DNA, but not in the adjacent normal colorectal mucosa, of most individuals with germline, mismatch repair-gene mutations (AGA, 2001). Microsatellites are repeating sequences of bases, found throughout the genome. Their function is unknown. Tumor DNA that shows alterations in microsatellite regions indicates probable defects in mismatch repair genes, possibly due to somatic changes. This microsatellite instability can suggest the diagnosis of HNPCC (Aaltonen, 1993 [cited in: Genetics of Colon Cancer, NCI, 2003]). MSI has been found in over 90% of HNPCC meeting the Amsterdam criteria and in 15% of sporadic colorectal cancers (AGA, 2001). The role of microsatellites in colorectal cancer led to the development of the Bethesda Guidelines, which provide clinical direction for the use of MSI testing. The Bethesda Criteria are intended to help identify tumors that should be tested for microsatellite instability, thereby identifying HNPCC patients. Affected individuals whose tumors are found to manifest a high frequency of MSI (MSI-H) are considered for further germline mutation analysis. The American Gastroenterological Association recommends, "MSI testing using the Bethesda markers should be performed on the tumor tissue of individuals putatively affected with HNPCC" (AGA, 2001). If the tumor is classified as MSI-H, then there is an increased likelihood that the family has HNPCC, and genetic testing is conducted to look for mismatch repair-gene mutations. This testing may be useful in individuals from smaller families or when family history is unknown.

Immunohistochemistry

Another method used to prescreen high-risk individuals for further germline mutation analysis is immunohistochemistry (IHC) testing for MLH1 and MSH2 expression. IHC testing may identify which gene to target for analysis. While some evidence in the scientific literature suggests that IHC testing may be as reliable as MSI testing in prescreening patients for mutation analysis, the data are still insufficient to draw conclusions regarding the role this testing method should play in routine practice.

Specialty Organization Guidelines for HNPCC/Lynch Syndrome Genetic Testing

At a 1990 meeting of the International Collaborative Group (ICG), research criteria were established for defining HNPCC families. These criteria are referred to as the Amsterdam Criteria. While the original criteria developed in 1990 provided a general approach to identifying HNPCC families, they are now considered too stringent and not sufficiently comprehensive. These criteria exclude individuals with HNPCC from small families with limited documented family history, as well as patients with HNPCC-related extracolonic cancer. A number of such families have been reported that do not have germline, mismatch repair-gene mutations (NCI, 2003).

The Bethesda Guidelines were developed in 1996 by a National Cancer Institute Workshop to identify tumors that should be tested for MSI, thus identifying HNPCC patients. These criteria were intended to be more sensitive than the Amsterdam criteria in identifying individuals who should be considered for HNPCC testing. To consider revision and improvement of the Bethesda Guidelines, another HNPCC workshop was held at the National Cancer Institute in Bethesda, Maryland, in 2002. The workshop included lectures based on current literature about HNPCC and MSI testing; presented issues relating to the performance, sensitivity and specificity of the Bethesda Guidelines; outlined the revised Bethesda Guidelines for identifying individuals at risk for HNPCC; and recommended criteria for MSI testing (Umar, 2004).

The Revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI) state that tumors from patients with colorectal cancer should be tested for MSI in the following situations and subsequent genetic testing conducted to confirm a mutation in one of the genes responsible for HNPCC in the following situations:

- The patient is younger than age 50.
- The patient has multiple HNPCC-associated tumors in the colon or in other areas caused by the same mutations, either at the same time or occurring over a period of time.
- A patient younger than age 60 had colorectal cancer that has microscopic characteristics that are often indicative of MSI.

- A patient has one or more first-degree relatives who had an HNPCC-related tumor at age 50 or younger.
- A patient has two or more first- or second-degree relatives who had HNPCC-related tumors at any age.

Recommendations for the process of molecular evaluation of patients identified as at risk according to the Bethesda Guidelines (Umar, 2004):

- The optimal approach to evaluation is microsatellite instability (MSI) or immunohistochemical (IHC) analysis of tumors, followed by germline MSH2/MLH1 testing in patients with MSI-H tumors or tumors with a loss of expression of one of the mismatch repair genes.
- After the mutation is identified, at-risk relatives should be referred for genetic counseling and tested if they wish.
- An alternative approach, if tissue testing is not feasible, is to proceed directly to germline analysis of the MSH2/MLH1 genes.
- If no mismatch repair-gene mutation is found in a proband with an MSI-H tumor and/or a clinical history of hereditary nonpolyposis colorectal cancer (HNPCC), the genetic test result is non-informative. The patients and the at-risk individuals (i.e., relatives) should be counseled as if HNPCC was confirmed and high-risk surveillance should be undertaken.
- There is a need to assure patients of confidentiality to allay fears related to discrimination based on genetic status.

The limitations of the Amsterdam Criteria, together with the acknowledgement that the Bethesda Guidelines are less specific than the Amsterdam criteria, led to the development of revised criteria, referred to as the Amsterdam II Criteria, in 1999 and the revised Bethesda Guidelines in 2004.

Summary of Evidence for HNPCC/Lynch Syndrome Genetic Testing

Evidence from the published, peer-reviewed scientific literature and consensus from the literature (including the American Gastroenterological Association, National Cancer Institute, and National Comprehensive Cancer Network) indicate that genetic testing for HNPCC mutations in affected patients is appropriate for individuals who meet either the Bethesda Guidelines or the Amsterdam II Criteria. Genetic testing of unaffected individuals is generally considered appropriate in those patients who have a first- or second-degree relative with a known HNPCC mutation. There is good evidence indicating that genetic testing for HNPCC in these individuals may improve health outcomes. Clinical benefits include identifying patients who will require increased surveillance, targeting surveillance methods, and targeting prophylactic, surgical options.

MSI tumor sample testing for MSH2 and MLH1 expression is generally considered medically necessary as an initial screen for patients affected with colorectal cancer who meet the Bethesda Guidelines, in order to identify those patients who should proceed with HNPCC testing. Insufficient evidence exists to support the use of IHC testing as a method to prescreen patients for further HNPCC mutation analysis.

Management/Intervention Strategies for Patients with Known HNPCC/Lynch Syndrome Mutations

Only one small controlled trial of colorectal cancer screening in HNPCC individuals has been reported. Nonetheless, several aspects of the biological behavior of HNPCC suggest how the approach to surveillance in individuals with known HNPCC mutations may differ from that taken with people at average risk.

- **Increased surveillance** (screening begins earlier in life and with shorter intervals between screenings than general population):
 - Colonoscopic screening should start earlier in life, and be performed as frequently as every 1-2 years.
 - The fact that 60-70% of HNPCC cancers occur in the right colon suggests that sigmoidoscopy alone may not be the appropriate screening tool. Therefore, complete structural examination of the colon should be performed by colonoscopy or double-contrast barium enema.

- Screening should be performed at shorter intervals, since the progression to adenoma from normal mucosa is more rapid than in average-risk patients
 - Annual endometrial and ovarian cancer screening (CA-125, endometrial aspiration, transvaginal ultrasound) should begin by age 25, because patients with HNPCC are at increased risk of other cancers, especially of the endometrium and ovary. According to the NCI, the level of evidence for this recommendation is 5.
- **Surgery:** No controlled studies have been reported regarding the benefit of prophylactic surgery in at-risk HNPCC carriers. Nonetheless, an expert panel convened by NIH recommended the following:
 - Once adenomas or adenocarcinomas have been identified, some experts recommend surgical options: subtotal colectomy; total abdominal colectomy with ileorectal anastomosis, or proctocolectomy; or endoscopic polypectomy with follow-up colonoscopy. The most appropriate option depends on individual circumstances.
 - Some experts recommend offering women with HNPCC and identified adenomas a prophylactic option of hysterectomy with bilateral salpingo-oophorectomy. These experts also recommend that counseling include thoughtful discussion of childbearing plans, the psychosocial effects of prophylactic surgery, the long-term effects of hormone replacement therapy (HRT), and the uncertainties concerning the efficacy of prophylactic surgery as a means of reducing the risk of endometrial or ovarian cancer. According to the NCI, the level of evidence for this recommendation is 5.

Genetic Counseling

Patients should be advised that genetic testing for susceptibility to colorectal cancer is a multi-step process that includes risk assessment, pre-testing education, and follow-up counseling after the testing results are known. Pre- and post-testing genetic counseling, provided by a licensed or certified genetic counselor or physician with specific training in cancer genetics, relies on education, risk assessment and risk management to help individuals and their families cope with a disorder or heightened risk of a disorder. Genetic counseling may also promote adherence to cancer surveillance recommendations.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
83890	Molecular diagnostics; molecular isolation or extraction
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892	Molecular diagnostics; enzymatic digestion
83893	Molecular diagnostics; dot/slot blot production
83894	Molecular diagnostics; separation by gel electrophoresis (e.g., agarose, polyacrylamide)
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (e.g., Southern, Northern)
83898	Molecular diagnostics; amplification of patient nucleic acid (e.g., PCR, LCR), single primer pair, each primer pair
83901	Molecular diagnostics; amplification of patient nucleic acid, multiplex, each multiplex reaction
83902	Molecular diagnostics; reverse transcription
83903	Molecular diagnostics; mutation scanning, by physical properties (e.g., single strand conformational polymorphisms (SSCP), heteroduplex, denaturing gradient gel electrophoresis (DGGE), RNA'ase A), single segment, each
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each

83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83906	Molecular diagnostics; mutation detection by allele specific translation, single segment, each segment
83912	Molecular diagnostics; interpretation and report

HCPCS Codes	Description
S3828	Complete gene sequence analysis; MLH1 gene
S3829	Complete gene sequence analysis; MSH2 gene
S3830	Complete mlh1 and mlh2 gene sequence analysis for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing
S3831	Single-mutation analysis (in an individual with a known mlh1 and mlh2 mutation in the family) for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing
S3833	Complete APC gene sequence analysis for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP
S3834	Single-mutation analysis (in individuals with a known APC mutation in the family) for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP

ICD-9-CM Diagnosis Codes	Description
153.0	Malignant neoplasm of hepatic flexure
153.1	Malignant neoplasm of transverse colon
153.2	Malignant neoplasm of descending colon
153.3	Malignant neoplasm of sigmoid colon
153.4	Malignant neoplasm of cecum
153.5	Malignant neoplasm of appendix
153.6	Malignant neoplasm of ascending colon
153.7	Malignant neoplasm of splenic flexure
153.8	Malignant neoplasm of other specified sites of large intestine
153.9	Malignant neoplasm of colon, unspecified
154.0	Malignant neoplasm of rectosigmoid junction
154.1	Malignant neoplasm of rectum
154.2	Malignant neoplasm of anal canal
154.3	Malignant neoplasm of anus, unspecified
154.8	Malignant neoplasm of rectum, rectosigmoid junction, and anus, other
211.3	Benign neoplasm of colon (adenomatous polyposis)
211.4	Benign neoplasm of rectum and anal canal
V10.00	Personal history of malignant neoplasm of gastrointestinal tract, unspecified
V10.05	Personal history of malignant neoplasm of large intestine
V10.06	Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus
V16.0	Family history of malignant neoplasm of gastrointestinal tract

***Current Procedural Terminology (CPT®) ©2003 American Medical Association: Chicago, IL.**

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