



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing for Susceptibility to Colorectal Cancer

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Coverage Policy

CIGNA covers genetic testing for susceptibility to colorectal cancer as medically necessary for ANY of the following indications:

- Familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP) genetic testing is covered in EITHER of the following situations:
 - for confirmatory testing of individuals with a personal history of suspected FAP or AFAP
 - for predictive testing when the individual has a first- or second-degree relative* with a disease-causing mutation for FAP or AFAP (gene APC)
- MYH-associated polyposis (MAP) genetic testing (gene MutY human homolog [MYH]) is covered in EITHER of the following situations:
 - for confirmatory testing for individuals with a history of adenomatous polyposis (>10 adenomas) and EITHER of the following indications:
 - Findings consistent with recessive inheritance
 - Negative APC mutation testing
 - for predictive testing when an individual has a sibling with known MYH polyposis.
- Hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing is covered in EITHER of the following situations:
 - for confirmatory testing when the Amsterdam II criteria or the revised Bethesda guidelines** are met or endometrial cancer is diagnosed before age 50

- for predictive testing when a individual has a first- or second-degree relative* with a disease-causing mutation for HNPCC (genes MLH1, MSH2, MSH6, PMS2)

- Microsatellite instability (MSI) testing or immunohistochemical (IHC) analysis of the tumor (colorectal and/or endometrial) is covered as an initial screen in individuals with colorectal cancer who meet the revised Bethesda guidelines**, in order to identify those individuals 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 his/her 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 his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

**Amsterdam II criteria	**Revised Bethesda guidelines
<p>At least three relatives must have a cancer associated with HNPCC (colorectal, cancer of endometrial, small bowel, ureter and renal pelvis); and ALL of the following criteria should be present:</p> <ul style="list-style-type: none"> • one must be a first-degree relative of the other two • at least two successive generations must be affected • at least one of the relatives with cancer associated with HNPCC should be diagnosed before age 50. • FAP should be excluded in the colorectal cancer cases (if any) • tumors should be verified whenever possible 	<p>Individual must meet ONE of the following criteria:</p> <ul style="list-style-type: none"> • 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 individual 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

CIGNA does not cover genetic testing for susceptibility to colorectal cancer for EITHER of 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 colorectal cancer in the general population
- genetic testing for the APC1307K missense mutation

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or licensed or certified genetic counselor.

General Background

The etiology of colorectal cancer is heterogeneous and may be influenced by both the environment and genetics. Genetic mutations have been identified as the cause of inherited cancer risk in some colon cancer prone families. Mutations on several genes are associated with hereditary colorectal cancer. The adenomatous polyposis coli (APC) gene has been linked to APC-associated polyposis conditions, including familial adenomatous polyposis (FAP) and attenuated FAP (AFAP). MYH-associated polyposis (MAP) is caused by biallelic germ line mutations in the MutY human homolog (MYH) gene. DNA mismatch repair genes, MLH1, MSH2, MSH6, and PMS2 appear connected to hereditary nonpolyposis colorectal cancer (HNPCC).

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

FAP and AFAP are inherited in an autosomal dominant manner. Approximately 75–80% of individuals with these conditions have an affected parent. Offspring of an affected individual have a 50% risk of inheriting the altered APC gene.

FAP 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. Additional findings include congenital hypertrophy of retinal pigment epithelium (CHRPE), osteomas, supernumerary teeth, odontomas, desmoids, epidermoid cysts, duodenal and other small bowel adenomas, gastric fundic gland polyps. There is also increased risk of medulloblastoma, papillary carcinoma of the thyroid, hepatoblastoma, pancreatic and gastric cancers. 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 (National Comprehensive Cancer Network® [NCCN®], 2010).

AFAP, an attenuated variety of FAP, is characterized by a significant risk for colon cancer, but fewer colonic polyps than classic FAP. An average of 30 polyps is seen in AFAP. The polyps tend to be found more proximally in the colon than in classic FAP. The average age of colon cancer diagnosis in individuals with AFAP is age 50–55 years, approximately 10–15 years later than in those with classic FAP, but earlier than that seen in individuals with sporadically occurring colon cancer. Mutations of the APC gene are also associated with AFAP. APC mutation testing is positive in approximately 60% of cases (NCCN, 2010).

Most cases of FAP and AFAP are associated with mutations in the 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. The penetrance of FAP in terms of colonic adenomatous polyposis and colon cancer is virtually 100% in untreated individuals.

Management and surveillance will be dependent upon the age and adenoma burden. The NCCN includes guidelines for patients with personal history of FAP that includes time-frames for screening with flexible sigmoidoscopy or colonoscopy, timing for surgery, and recommendations for management and surveillance for patients who have undergone surgery (NCCN, 2010).

Literature Review 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 evidence demonstrating that identifying carriers of the APC genetic mutations affects health outcomes positively. Clinical benefits include the ability to target surveillance methods, to more accurately estimate cancer risk, 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 (AGA), American College of Medical Genetics (ACMG), NCCN and National Cancer Institute (NCI). It is generally accepted that genetic testing for FAP and AFAP is appropriate for the following purposes:

- to confirm the diagnosis of FAP and AFAP in an affected patient
- to provide predictive testing for at-risk relatives of AFAP and FAP-affected patients with known APC gene mutation

MYH-Associated Polyposis (MAP)

MYH-Associated Polyposis (MAP), also known as MUTYH-associated polyposis, is a recently described syndrome that is also characterized by adenomatous polyps. It is an autosomal-recessive syndrome. It is estimated that MAP is responsible for 1.4% of all adenomatous polyposis and 20% of adenomatous polyposis without mutation of the APC gene (Lefevre, et al., 2006). MAP is caused by biallelic mutations in the MutY human homolog (MYH) gene. Generally, most individuals with MAP will have less than 100 polyps (approximately 15–100 polyps). The median age of presentation is in the mid forties to late fifties. The NCCN notes that screening and surveillance for these individuals are based on limited retrospective data, with genetic counseling and testing recommended for siblings of affected patients, as well as for patients with adenomatous

polyposis (more than 10 adenomas) whose family is consistent with recessive inheritance (NCCN, 2010). It is also noted that testing for APC mutation usually precedes testing for MYH mutations, except in families where only siblings are affected, which suggests recessive inheritance.

Management and surveillance will be dependent upon the personal and family history, and adenoma burden. The National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™) for colorectal cancer screening include recommendations for asymptomatic patients with family history of MAP, and mutation status is unknown or biallelic MYH mutations are known and for patients with personal history of adenomatous polyposis and positive MYH testing. The guidelines include recommendations for timeframes for colonoscopy, upper endoscopy, duodenoscopy and counseling for surgery (NCCN, 2010).

Literature Review for MYH-Associated Polyposis (MAP) Genetic Testing: Evidence in the published, peer-reviewed scientific literature indicates that genetic testing for mutations in the MYH gene is appropriate for a specific subset of individuals who have been identified as at high-risk for MAP. Several case studies have been published that demonstrate MYH mutations predispose individuals to polyposis and colorectal cancer. The studies indicate that testing of MYH is indicated for diagnosis and calculation of the level of risk in relatives (Sieber, et al., 2003; Bouguen, et al., 2007; Lefevre, et al., 2006).

APC11307K missense mutation: A missense mutation of the APC gene known as APC11307K has been discovered as a cause of an undefined proportion of familial colorectal cancer in a specific ethnic group (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 and in up to 28% of such patients who also have a positive family history of colon cancer (ACMG/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], 2010). While genetic testing for this mutation is possible, the clinical utility of testing has not been established. According to the NCI, "On the basis of currently available data, it is not yet known whether the I1307K carrier state should guide decisions regarding the age at which to initiate screening, frequency of screening, or choice of screening strategy" (NCI, 2010). The NCCN practice guidelines for Colorectal Screening note that testing for this mutation has been intentionally excluded from the guidelines since there is "very little evidence to date indicating what kinds of screening guidelines should be offered to individuals with this mutation." (NCCN, 2010)

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

HNPCC is also known as Lynch syndrome. It 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 occurring at an early age (i.e., approximately age 45) (NCCN, 2010), 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. Cancer of the endometrium is the second most common cancer observed in Lynch syndrome families with initial estimates of cumulative risk in Lynch syndrome carriers of 30% to 39% by age 70 years (NCI, 2010). 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, MSH6 and rarely PMS2). The MSH2 and MLH1 genes are thought to account for the majority of the mutations. HNPCC accounts for 2–3% of all colorectal cancer cases and is associated with a lifetime risk of colon or rectal cancer approaching 80% (NCCN, 2010). These mismatch repair genes are classified as caretaker genes because their function is to maintain the fidelity of DNA during replication. It is essential to obtain a detailed family history, including: parents, children, siblings/half-siblings, aunts and uncles, grandparents, great-grandparents, cousins, nieces, and nephews. The minimal data set on each relative would include type of cancer (i.e., medical record of cancer strongly encouraged), ethnicity/country of origin, suspected colon cancer syndromes, additional syndrome-specific features (e.g., Muir-Torre, Turcot, Peutz-Jeghers, juvenile polyposis), and all other inherited conditions and birth defects (NCCN, 2010).

In general, genetic testing for HNPCC is not recommended for at-risk individuals under the age of 18. It has been noted that individuals have been diagnosed with cancer at very young ages, and it is recommended that

screening begin ten years before the earliest age of onset in the family. Therefore, in some situations, screening may need to begin before the age of 18 years (Kohlmann and Gruber, 2006; NCCN, 2010).

Due to the high risk of colorectal cancer in patients with known HNPCC mutation, intensive screening is essential, although the exact intervals have not been fully established in clinical trials. The recommendations in this area are based on the best evidence to date, but more data is still needed (NCCN, 2010). The NCCN publishes guidelines that include timeframes and methods for surveillance for patients with HNPCC mutations. The surgical management of a patient with HNPCC should be individualized. No controlled studies have been reported regarding the benefit of prophylactic surgery in at-risk HNPCC carriers. An expert panel convened by National Institute of Health (NIH) provides recommendations for surgical treatment (NCI, 2010).

Amsterdam Criteria/Bethesda Guidelines: At a 1990 meeting of the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC), 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, 2010). In 1999, the criteria were revised to include other recognized cancers within HNPCC (i.e., colorectal, cancer of the endometrium, small bowel, ureter, or renal pelvis) and are referred to as the Amsterdam II criteria.

The Bethesda guidelines were developed in 1996 by an NCI Workshop to identify tumors that should be tested for MSI. These criteria were intended to be more sensitive than the Amsterdam criteria in identifying individuals who should be considered for HNPCC testing. In 2002, the NCI sponsored another HNPCC workshop to consider revision and improvement of the Bethesda guidelines. 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 MSI state that those tumors from patients with colorectal cancer should be tested for MSI in the following situations and subsequent genetic testing to confirm a mutation in one of the genes responsible for HNPCC in the following situations (Umar, 2004):

- 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

The Bethesda guidelines include the following recommendations for the process of molecular evaluation of patients identified as at-risk based on Bethesda guidelines (Umar, 2004):

- The optimal approach to evaluation is MSI or 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 HNPCC, the genetic test result is noninformative. 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.

Microsatellite Instability (MSI): 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. Tumor DNA that shows alterations in microsatellite regions indicates probable defects in mismatch repair genes, possibly due to somatic changes. The changes found in MSI testing can suggest the diagnosis of HNPCC (NCI, 2010). MSI has been found in over 95% 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 guidelines 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. MSI is classified as MSI-H if there are more than 30% of the markers showing instability; MSI-low (L) if fewer than 30% of the markers show instability and MSI-stable (S) is 0% of the markers show instability. The AGA 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 (IHC) Testing: IHC testing is another method used to prescreen high-risk individuals for further germline mutation analysis. IHC testing refers to staining for protein expression of the four mismatch genes known to be mutated in HNPCC. A normal IHC test implies that all four mismatch repair proteins are normally expressed and thus no underlying mismatch repair gene mutation is present (NCCN, 2010). An abnormal test means that one of the proteins is not expressed, and an inherited mutation may be present in the related gene. IHC testing may identify which gene to target for analysis (NCI, 2010). Since a molecular lab is not needed for this testing, it has been noted in the literature that it is the most clinically available test for detection of the proteins encoded by genes MLH1, MSH2, and MSH6 (Kohlmann and Gruber, 2006).

Molecular Genetic Testing for HNPCC: If a patient meets Bethesda guidelines, then examination of tumor tissue is indicated. Endometrial cancer diagnosed at younger than 50 years of age is not included in the Bethesda guidelines, however recent evidence suggests that these individuals should also be evaluated for Lynch syndrome (NCCN, 2010; Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, 2009). MSI and IHC are used as prescreening tests in tumor tissue to select individuals eligible for mutation analysis in blood. This can avoid unnecessary, expensive and time-consuming DNA-analyses (Hendriks, et al., 2006). Both of these techniques fail to be 100% accurate and cannot provide definite answers about the presence and location of a pathogenic mutation. They need to be followed by germline analysis in one of several mismatch repair genes. Molecular genetic testing is appropriate in individuals who meet Bethesda guidelines and have MSI-H tumors and/or have abnormal IHC. In patients who meet Amsterdam II criteria or if suitable tumor tissue is not available, then germline testing can be performed initially (Kohlmann and Gruber, 2006). Patients meeting Amsterdam II criteria, revised Bethesda guidelines, or with endometrial cancer diagnosed before age 50, should be referred for genetic counseling and assessment for genetic testing (NCCN, 2010).

COLARIS Test®

The COLARIS test (Myriad Genetics, Inc., Salt Lake City, UT) is a patented test that assesses a person's risk of developing colorectal cancer. According to the Myriad website, the test is available in the following options:

- COLARIS test detects mutations in MLH1, MSH2, and MSH6 genes.
- COLARIS AP test detects mutations in the APC and MYH genes

Literature Review for HNPCC

Evidence in the published, peer-reviewed scientific literature indicates that genetic testing for mutations in the mutations in the MLH1, MSH2, MSH6, and PMS2 genes is appropriate for a specific subset of individuals who have been identified as at high-risk for HNPCC. Several studies have been published that demonstrate these mutations lead to risk for HNPCC. The studies indicate that genetic testing of MLH1, MSH2, MSH6, and PMS2 genes is indicated for diagnosis and calculation of the level of risk in relatives (Pinol, et al., 2005; Hampel, et al., 2005).

Professional Societies/Organizations

American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG):

The ACMG and ASHG published a joint statement regarding genetic testing for colon cancer. The statement notes that molecular testing has the potential to improve management of mutation carriers. In addition, it is noted that molecular diagnostic testing can assist in improving characterization of syndromes or even split syndromes. The statement notes that this is a very active area of research, and genetic tests are part of the spectrum of clinical information gathering through which management options can be developed (ACMG/ASHG, 2000).

American Gastroenterological Association (AGA): The AGA published a medical position statement regarding hereditary colorectal cancer and genetic testing. The statement noted that integrating genetic testing into clinical practice provides multiple benefits to individuals in families with histories of colorectal cancer, including (AGA, 2001):

- earlier detection of colorectal neoplasm and prevention of cancer
- removal of patient uncertainty
- greater choice of surgical and other intervention options
- elimination of unnecessary screening
- provision of information for making family and career decisions

The statement included the following recommendations regarding testing strategy for HNPCC:

- pretest genetic counseling and informed consent for genetic testing of both affected and at-risk relatives
- IHC for MSH2 and MLH1 combined with MSI testing on tumor tissue of individuals meeting revised Bethesda guidelines
- consideration of germline testing for mutations in the MSH2 and MLH1 genes following MSI-H result in tumor DNA
- targeting of a specific gene according to the IHC result
- if the presence of a deleterious gene is found in an affected family member it will provide true positive or negative results in at-risk relatives undergoing genetic testing
- absence of a deleterious gene in an affected family member provides inconclusive or uninformative results in at-risk relatives
- MSI-L or MSS results indicate a low likelihood of harboring mismatch repair gene mutations and further genetic testing is not pursued
- consideration of initial germline testing in an affected person when MSI testing is not possible or the family/individual meets any of the first three conditions of the revised Bethesda guidelines

Starting the testing process with at-risk family members when an affected family member is not available for evaluation can provide only positive or inconclusive results. True negative results can only be obtained if another at-risk family member tests positive for a mutation. This is not a preferred strategy due to the high likelihood of an inconclusive test result (AGA, 2001).

American Society of Clinical Oncology (ASCO): The ASCO published a policy statement regarding genetic testing for cancer susceptibility. The ASCO statement includes recommendations that genetic counseling and testing be offered when (ASCO, 2003):

- The individual has personal or family history and the features suggestive of a genetic cancer susceptibility condition
- The genetic test can be adequately interpreted
- The test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer

In addition, the ASCO recommends that genetic testing only be done in the setting of pre- and post-test counseling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities. It is also noted by the ASCO that none of the cancer susceptibility tests currently available is as yet appropriate for screening of asymptomatic individuals in the general population. However, in the setting of clinically defined cancer susceptibility syndromes or suggestive individual cancer histories with or without family history information, the identification of a mutation in an affected member of the family may influence medical management and can be used as a critical baseline in the testing of other family members (ASCO, 2003).

American Society of Colon and Rectal Surgeons (ASCRS): The ASCRS published practice parameters for the identification and testing of patients at risk for dominantly inherited colorectal cancer. The document focused on risk recognition and assessment, and testing, screening, and surveillance. The guidelines addressed included the following (Church, et al., 2001):

- Take a family history, including number of affected relatives, relationship, and age at diagnosis.
- Document a suspicious pedigree, including confirmation of diagnoses with pathology reports, death certificates, or other medical records.
- Identify criteria for genetic testing, (e.g., the Amsterdam criteria).
- Determine who should be involved with these patients (e.g., patients may be referred to centers that have a registry or clinical program).
- Offer surveillance to families for whom genetic testing is not indicated.

National Comprehensive Cancer Network (NCCN): The NCCN published clinical practice guidelines regarding colorectal cancer screening. The guidelines include screening guidelines for hereditary predisposition to colorectal cancer.

For genetic counseling and testing for HNPCC, the guidelines include the following (NCCN, 2010):

- Determine if:
 - revised Bethesda guidelines are met
 - Amsterdam criteria are met
 - endometrial cancer diagnosed at younger than 50 years of age
 - there is known Lynch syndrome in family
- If the deleterious Lynch syndrome is known, then perform genetic testing for familial mutation
- If there Lynch syndrome mutation is not known, then:
 - if tumor is available, consider both IHC and MSI testing
 - if no tumor is unavailable or insufficient tumor, than in affected relative consider testing for MLH1 and MSH2, then MSH6, and possibly PMS2 if a mutation is not found in the first three genes
- If the familial mismatch mutation is known, then consider genetic testing of at-risk family members
- If not tested, or no familial mutation found, or mutation of unknown significance found then tailor surveillance based on individual and family risk assessment

For genetic counseling and testing for adenomatous polyposis syndromes, including FAP, and AFAP, the guidelines include the following (NCCN, 2010):

- FAP Inclusion criteria include:
 - Presence of over 100 polyps, or fewer polyps at younger ages, especially in family known to have FAP
 - Autosomal dominant inheritance
 - Possible associated additional findings, including:
 - Congenital hypertrophy of retinal pigment epithelium (CHRPE)
 - Osteomas, supernumerary teeth, odontomas
 - Desmoids, epidermoid cysts
 - Duodenal and other small bowel adenomas
 - Gastric fundic gland polyps
 - Increased risk of meduloblastoma, papillary carcinoma of the thyroid (<2%) or hepatoblastoma (usually ≤age 5 years)
 - Pancreatic cancers (<1%)
 - Gastric cancers (<1%)
- AFAP inclusion criteria include:
 - Fewer than 100 adenomas (range 0 – >1000) (average of 30 polyps)
 - Frequent right-sided distribution of polyps
 - Adenomas and cancers at age older than classic FAP (i.e., mean cancer age greater than 50)
 - Upper GI findings and thyroid cancer risk is similar to classic FAP
 - Other extraintestinal manifestations, including CHRPE and desmoids are rare
- If personal history is positive, then refer to genetic screening
- If family mutation is known, then refer at-risk family members to genetic screening

For genetic counseling and testing for MAP, the guidelines include the following (NCCN, 2010):

- MAP inclusion criteria include:
 - Polyposis or colon cancers consistent with autosomal recessive (i.e., parents unaffected, siblings affected)
 - Fewer than 100 adenomas (range 0–100s and uncommonly >1000)
 - Adenomas and colorectal cancer at age older than classical FAP (median age >50)
 - Duodenal adenomas are uncommon
 - Attenuated polyposis with negative APC gene mutation
- If personal history is positive, then refer to genetic screening
- Testing for APC gene mutations usually precedes testing for MYH mutations, except in families in which only siblings are affected
- Recommend genetic counseling and testing for germ line MYH mutations for siblings of affected patients
- If family mutation is known, then refer at-risk family members to genetic screening

Society of Gynecologic Oncologists (SGO): published guidelines for risk assessment for inherited gynecologic cancer predispositions (Lancaster, et al., 2007). The guidelines include the following recommendations:

Individuals with greater than approximately 20–25% chance of having an inherited predisposition to endometrial, colorectal and related cancers and for whom genetic risk assessment is recommended include:

- Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria
- Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e. microsatellite instability (MSI) or immunohistochemical loss of expression of MLH1, MSH2, MSH6 or PMS2)
- Patients with a first or second degree relative with a known mismatch repair gene mutation

Individuals with greater than approximately 5–10% chance of having an inherited predisposition to endometrial, colorectal and related cancers and for whom genetic risk assessment may be helpful include patients with:

- endometrial or colorectal cancer diagnosed prior to age 50
- endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor at any age
- endometrial or colorectal cancer and a first degree relative with a Lynch/HNPCC-associated tumor diagnosed prior to age 50
- colorectal or endometrial cancer diagnosed at any age with two or more first or second degree relatives† with Lynch/HNPCC-associated tumors, regardless of age
- a first- or-second degree relative that meets the above criteria

Summary

Evidence from the published, peer-reviewed scientific literature and consensus from professional societies/organizations (e.g., the American Gastroenterological Association [AGA], National Cancer Institute [NCI], and National Comprehensive Cancer Network [NCCN]) indicate that genetic testing for hereditary nonpolyposis colorectal cancer (HNPCC) mutations in affected patients is appropriate for individuals who meet either the revised Bethesda guidelines or the Amsterdam II criteria or diagnosed with endometrial cancer before age of 50. 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. Clinical benefits include identification of patients who will require increased surveillance; targeting surveillance methods; targeting prophylactic, and surgical options.

Microsatellite instability (MSI) tumor sample testing for MSH2 and MLH1 expression and immunohistochemical (IHC) analysis is generally considered medically necessary as an initial screen for patients affected with colorectal cancer who meet the revised Bethesda guidelines. These tests are useful in identifying those patients who should proceed with HNPCC molecular genetic testing.

Evidence in the published peer-reviewed scientific literature and professional societies/organizations (e.g., the AGA, NCI, and NCCN) 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 familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP). Evidence in the published peer-reviewed scientific literature and NCCN practice guidelines indicate that genetic testing for mutations in the MYH gene is appropriate for a specific subset of individuals who have been identified as at high risk for MYH-Associated Polyposis (MAP).

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, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83893	Molecular diagnostics; dot/slot blot production, each nucleic acid preparation
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83902	Molecular diagnostics; reverse transcription
83903	Molecular diagnostics; mutation scanning, by physical properties (eg, 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 segment
83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83906	Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment
83907	Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen
83908	Molecular diagnostics; amplification, signal, each nucleic acid sequence
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis)
83912	Molecular diagnostics; interpretation and report
83913	Molecular diagnostics; RNA stabilization

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 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 – 153.9	Malignant neoplasm of colon
154.0 – 154.8	Malignant neoplasm of rectum, rectosigmoid junction, and anus
182.0	Malignant neoplasm of body of uterus, Corpus uteri, except isthmus
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
V10.42	Personal history of malignant neoplasm, Other parts of uterus
V16.0	Family history of malignant neoplasm of gastrointestinal tract
V26.31	Testing of female for genetic disease carrier status
V26.34	Testing of male for genetic disease carrier status

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	1/15/2008	0014	Genetic Testing for Susceptibility to Colorectal Cancer

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