Cigna Medical Coverage Policy

**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:
  - confirmatory testing of an individuals with a personal history of FAP or AFAP
  - predictive testing for an individual with a first- or second- or third 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:
  - confirmatory testing for an individual with autosomal recessive inheritance of MAP phenotype and/or with a history of adenomatous polyposis (>10 adenomas) and **EITHER** of the following indications:
    - negative APC mutation testing
    - negative hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome screening and/or testing
  - predictive testing when an individual has a sibling with known MYH polyposis

- Hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing is covered in **ANY** of the following situations:
  - confirmatory testing of **EITHER** of the following:
o individuals with a HNPCC-associated cancer when the Amsterdam II criteria or the revised Bethesda guidelines** are met
o endometrial cancer is diagnosed before age 50

➢ predictive testing in an unaffected individual with BOTH of the following:
  o an affected first-degree relative whose cancer diagnosis meets the Amsterdam II criteria or revised Bethesda guidelines**
  o tumor testing results are not available for at-risk first-, second- or third-degree relatives

➢ predictive testing when the individuals has a first-, second-, or third-degree relative* with a disease-causing mutation for HNPCC (genes MLH1, MSH2, MSH6, PMS2, EPCAM/TACSTD1)

➢ 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 and/or endometrial cancer or colorectal adenomas (when malignant tissue is not available) for EITHER of the following indications:
  o individual with colorectal or endometrial cancer whose family meets the Amsterdam II criteria or revised Bethesda guidelines**
  o individual with stage II colorectal cancer for whom adjuvant single-agent fluoropyrimidine chemotherapy is being considered and where the results will be used in treatment decision-making

➢ Tumor testing for the BRAF V600E and MLH1 promoter hypermethylation is covered for individuals with colon cancer when IHC tumor screening identified a loss of MLH1 expression.

*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.
A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual's great-grandparents and first-cousins.

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<th><strong>Amsterdam II criteria</strong></th>
<th><strong>Revised Bethesda guidelines</strong></th>
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<td>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:</td>
<td>Individual must meet ONE of the following criteria:</td>
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<td>• one must be a first-degree relative of the other two</td>
<td>• colorectal cancer diagnosed under age 50</td>
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<td>• at least two successive generations must be affected</td>
<td>• presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age</td>
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<td>• at least one of the relatives with cancer associated with HNPCC should be diagnosed before age 50.</td>
<td>• colorectal cancer with the MSI-H histology diagnosed in a individual who is under age 60</td>
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<td>• FAP should be excluded in the colorectal cancer cases (if any)</td>
<td>• colorectal cancer diagnosed with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers diagnosed under age 50</td>
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<td>• tumors should be verified whenever possible</td>
<td>• colorectal cancer diagnosed in two or more first- or second-degree* relatives with an HNPCC-related tumor, regardless of age</td>
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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 APCI1307K missense mutation
All individuals undergoing genetic testing for susceptibility to colorectal cancer should have both pre- and post-test genetic counseling with a board-certified or board-eligible medical geneticist or a 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, along with gene EPCAM (also known as TACSTD1) appear connected to hereditary nonpolyposis colorectal cancer (HNPCC).

Genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Post genetic testing counseling should be planned. The genetic counseling should be provided by an independent specialty-trained professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional who is unaffiliated with the genetic testing lab performing the test(s). The genetic counselor may assist in determining if the individual is the best candidate for genetic testing. A person can be the best candidate if they have the most suspicious phenotype, or if the relative with the most suspicious phenotype is not available.

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®], 2011).

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, 2011).

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 patient’s who have undergone surgery (NCCN, 2011).
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).

Genetic Testing for FAP/AFAP
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 of gene APC for at-risk relatives of AFAP and FAP-affected patients with known APC gene mutation. Single site testing is indicated unless the individual meets criteria for testing of other genes.

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, 2011).

The NCCN notes that testing for APC mutation usually precedes testing for MYH mutations, except in families where only siblings are affected, which suggests recessive inheritance (NCCN, 2011). There may be cases of MAP where it is not associated with polyps. In some cases with no polyps or low polyp, it may be appropriate to perform Lynch syndrome evaluation. For predictive testing of individuals with a sibling with a known mutation, testing for the familial mutation only is indicated unless the individual meets criteria for other testing.

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, 2011).

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).

APCI1307K missense mutation: A missense mutation of the APC gene known as APCI1307K 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 APCI1307K 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], 2011a). 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, 2011a). 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, 2011)

**Hereditary Nonpolyposis Colorectal Cancer (HNPCC)/Lynch Syndrome**

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 occurring at an early age (i.e., approximately age 45) (NCCN, 2011), 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, 2011a). 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 (MMR) genes (MSH2, MLH1, MSH6 and PMS2). In addition, germline deletion within the gene EPICAM (also known as TACSTD1), which is not an MMR gene, can disrupt the MMR pathway. EPICAM deletions result in inactivating the adjacent MMR gene MSH2, even though MSH2 has not been mutated (Kohlmann and Gruber, 2011). The MSH2 and MLH1 genes are thought to account for the majority of the mutations. Fifty-per cent of Lynch syndrome is thought to be attributed to the MLHI gene; 40% to the MSH2 gene; 7–10% to the MSH6 gene; less than 5% to the PMS2 gene; and, approximately 1–3% to the EPICAM gene (Kohlmann and Gruber, 2011).

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, 2011). 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, 2011).

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, 2011; NCCN, 2011).

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, 2011). 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, 2011a).

**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, 2011a). 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.

**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, 2011). 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, 2011a). An advantage of IHC testing is that it is readily available at most centers and is technically easy to perform (Kohlmann and Gruber, 2011).

**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). Microsatellite 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, 2011a). 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.

**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, 2011; 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. When IHC/MSI is performed on a deceased relative's tumor, the tumor at the highest level of suspicion for HNPCC should be tested whenever possible, with colorectal cancer prioritized over endometrial cancer. IHC and MSI should be done sequentially—IHC should be ordered first, followed by MSI as a reflex test if protein expression is intact.

They need to be followed by germline analysis in one of several mismatch repair genes. Germline testing should be done sequentially—testing for MLH1 and MSH2 genes should be performed first, followed by reflex testing of gene MSH6 and then gene PMS2 if the previous results are normal. If this is also negative, genetic testing of MSH6 can be performed and then gene PMS2 if previous results are normal (Goodenberger, et al., 2011). When germline testing follows IHC testing, then only testing for the indicated gene should be performed. When germline testing is done due to a family history of a known mutation, only testing for the specific mutation should be performed. When IHC is not possible, MLH1 should be performed first, with reflex testing of MSH6 and then PMS2 if previous results are normal. EPCAM testing should only be performed unless indicated by IHC results.

Molecular genetic testing of the tumor for methylation and somatic BRAF mutations may help identify those tumors more likely to be sporadic than hereditary. Testing colon tumor tissue for abnormal methylation of MLH1 and for somatic BRAF mutations may identify tumors that are more likely to be sporadic than the result of a germline mutation in an MMR gene. If the findings from these and other tests of tumor tissue are consistent with Lynch syndrome, then germline molecular genetic testing can be pursued (Kohlmann and Gruber, 2011). BRAF mutations, the most common being Val600Glu (V600E), occur in 15% of colorectal cancers. BRAF mutations are thought to be rare in Lynch syndrome-related cancers and, thus, in general the presence of a BRAF mutation rules out the diagnosis of Lynch syndrome (Kohlmann and Gruber, 2011). The majority of MSI is caused by somatic methylation of the promoter region of MLH1 that silences gene expression in the tumor tissue; thus, the finding of MLH1 promoter methylation can often help eliminate the diagnosis of Lynch syndrome. BRAF mutations are not common in sporadic endometrial cancers—BRAF testing is not a helpful step for distinguishing sporadic endometrial cancers from those that are Lynch syndrome related.

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, 2011). Predictive testing may be considered in individuals with a first-, second-, or third-degree relative* with a disease-causing mutation for HNPCC (genes MLH1, MSH2, MSH6, PMS2, EPCAM/TACSTD1) (NCCN, 2012; Kohlmann and Gruber, 2011). Predictive testing may also be considered in unaffected individuals with a first-degree relative whose cancer diagnosis meets the meets the Amsterdam II criteria or revised Bethesda guidelines. The likelihood of an unaffected person having a mutation depends on that individual's degree of relatedness to an affected family member. A first-degree relative has a 50% chance of having inherited a mutation. Analysis suggests that testing unaffected individuals is worth pursuing in such instances because of the significant benefit for the family if a Lynch syndrome causative germline mutation is identified (Kohlmann and Gruber, 2011).

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, 2011).
The NCCN guidelines for colon cancer note that there is evidence that microsatellite instability is a marker of a more favorable outcome and decrease benefit from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease (NCCN, 2012). It is recommended to test for MMR genes in patients with stage II colon cancer in whom single-agent fluoropyrimidine chemotherapy is planned (NCCN, 2012; Ribic, et al., 2003; Sargent et al., 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, PMS2, and EPCAM 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 MLH1, MSH2, MSH6, PMS2 and EPCAM 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 these genes is indicated for diagnosis and calculation of the level of risk in relatives (Pinol, et al., 2005; Hampel, et al., 2005; Rumilla, et al., 2011; Kempers, et al., 2011).

**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; Robson, et al., 2010):

- 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; Robson, et al., 2010).

**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, 2011):

- 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, then 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, 2011):

- 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 medulloblastoma, 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, 2011):

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 considered appropriate in those patients with a relative with 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 are 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: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

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<th>Description</th>
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<tr>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>83909</td>
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<td>Molecular diagnostics; interpretation and report</td>
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<td>Molecular diagnostics; RNA stabilization</td>
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### HCPCS Codes

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<td>S3829</td>
<td>Complete gene sequence analysis; MSH2 gene</td>
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<td>S3830</td>
<td>Complete mhl1 and mhl2 gene sequence analysis for hereditary nonpolyposis</td>
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<td>ICD-9-CM Diagnosis Codes</td>
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<td>153.0 – 153.9</td>
<td>Malignant neoplasm of colon</td>
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<tr>
<td>154.0 – 154.8</td>
<td>Malignant neoplasm of rectum, rectosigmoid junction, and anus</td>
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<td>Malignant neoplasm of body of uterus, Corpus uteri, except isthmus</td>
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<td>V26.34</td>
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References


