POLICY STATEMENT:

I. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, genetic testing for inherited colorectal cancer is **medically appropriate** only when offered in a setting with adequately trained health care professionals to provide appropriate pre and post-test counseling and performed by a qualified laboratory for the following situations:

   A. **Lynch syndrome (LS) or (hereditary nonpolyposis colorectal cancer, (HNPCC))** (germline mutations of MLH1, MSH2, MSH6, PMS2, EPCAM).

      Testing should be performed in the affected (personal history of cancer) family member first; that individual has the highest likelihood for a positive test result. A negative result for an unaffected (an individual who does not have cancer) individual with a family history only is considered indeterminate (uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

      1. Unaffected (an individual who does not have cancer) individuals who have a first (siblings, parents, offspring) or second degree relative (grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings) with an identified Lynch syndrome mutation; or

      2. Women with endometrial cancer diagnosed at age less than 50 years.

      3. Individuals who meet the ANY of the following criteria *(please refer to the revised Bethesda criteria in the Description section)*:
         a. Individuals diagnosed with colorectal cancer before age 50; OR
         b. Presence of synchronous (two or more primary cancers detected simultaneously either preoperatively or in the resected specimen or within 3-6 months of each other) and metachronous (two or more primary cancers detected after an intervening interval; usually after 6 months) colorectal Lynch syndrome-associated tumors* regardless of age; OR
         c. Individuals with colorectal cancer with the MSI-H histology diagnosed in a patient less than age 60; OR
         d. Individuals with colorectal cancer and 1 or more first-degree relatives with colorectal cancer and/or Lynch syndrome-related cancer*; with 1 of the cancers was diagnosed at age less than 50 years; OR
         e. Individuals with colorectal cancer and colorectal cancer diagnosed in 2 or more first- or second-degree relatives with Lynch syndrome-related tumors* regardless of age.

      *LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers as well as sebaceous gland adenomas and keratocanthuras as seen in Muir-Torre syndrome.
4. Individuals who meet ALL of the following criteria (please refer to the Amsterdam II criteria listed in the Description section):
   a. 3 or more relatives with a histologically verified Lynch syndrome associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter or renal pelvis); AND
   b. 1 of whom is a first-degree relative of the other 2; AND
   c. Lynch syndrome associated cancer involving at least 2 generations; AND
   d. Cancer in one or more affected relatives diagnosed before 50 years of age; AND
   e. Familial adenomatous polyposis excluded in any cases of colorectal cancer.

   Modifications allow for small HNPCC families: these families must have two colorectal cancers in first-degree relatives involving at least 2 generations, with at least one individual diagnosed by age 55.

B. Microsatellite instability (MSI) test/ Immunohistochemical (IHC) of tumor tissue for expression of one of the 4 mismatch repair (MMR) genes is a screening option. MSI and IHC testing may also provide some additional information when Lynch syndrome testing is inconclusive.

1. Tumor tissue of patients with colon or endometrial cancer diagnosed at any age; OR

2. Tumor tissue of patients with multiple colon polyps with at least one adenomatous polyp and who meet ANY of the following criteria (please refer to the revised Bethesda Criteria in the Description section):
   a. Individuals diagnosed with colorectal cancer before age 50; OR
   b. Presence of synchronous (two or more primary cancers detected simultaneously either preoperatively or in the resected specimen or within 3-6 months of each other) and metachronous (two or more primary cancers detected after an intervening interval; usually after 6 months) colorectal Lynch syndrome-associated tumors* regardless of age; OR
   c. Individuals with colorectal cancer with the MSI-H histology diagnosed in a patient less than age 60; OR
   d. Individuals with colorectal cancer and 1 or more first-degree relatives with colorectal cancer and/or Lynch syndrome-related cancer*; with 1 of the cancers was diagnosed at age less than 50 years; OR
   e. Individuals with colorectal cancer and colorectal cancer diagnosed in 2 or more first- or second-degree relatives with Lynch syndrome-related tumors* regardless of age.

   *LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers as well as sebaceous gland adenomas and keratocanthomas as seen in Muir-Torre syndrome.

3. Absent MLH1 expression by IHC should be followed by tumor testing for the presence of BRAF V600E mutation (or with IHC for BRAF) or for hypermethylation. Those with a germline mutation are identified as LS patients.

C. MUTYH- associated polyposis (MAP)

1. An individual with a personal history of greater than or equal to 20 adenomas.

2. An individual with at least some adenomas who meet at least one of the following criteria:
   a. at least 5 serrated polyps proximal to the sigmoid colon with 2 or more of these being greater than 10 mm; or
   b. greater than 20 serrated polyps of any size, but distributed throughout the colon.
3. Asymptomatic siblings of individuals with known MUTYH-associated polyposis.

4. Individuals with a known deleterious MUYTH mutation in the family.

D. Adenomatous polyposis coli gene (APC) for familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP)

1. An individual with a personal history of greater than or equal to 20 colonic polyps at any individual examination; or

2. An individual with personal history of desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral CHRPE, or between 10-20 adenomas; or

3. In first-degree relatives (e.g., siblings, parents, offspring) of patients diagnosed with FAP or AFAP.

4. Individuals with a known deleterious APC mutation in the family.

E. Juvenile polyposis syndrome (JPS)

1. Patients meeting one of the following clinical diagnostic criteria for JPS:
   a. At least 3 to 5 juvenile polyps of the colon; or
   b. Multiple juvenile polyps found throughout the colon; or
   c. Any number of juvenile polyps in an individual with a family history of JPS

2. In first-degree relatives (e.g., siblings, parents, offspring) of patients diagnosed with JPS.

F. Peutz-Jeghers Syndrome (STK11) (2 or more of the following):

1. 2 or more Peutz-Jeghers-type hamartomatous polyps of the small intestine; or

2. Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; or


II. Genetic testing for inherited colorectal cancer is considered **not medically appropriate**:

A. If the genetic test is being done for knowledge only and that knowledge will not alter management or treatment of the patient.

B. If there is a high clinical likelihood that the patient has a specific disease and the screening or treatment will not be modified based on the genetic testing.

C. Genetic testing for inherited colorectal cancer when performed primarily for the medical management of other family members not covered by the affected member’s subscriber agreement.
III. Please refer to Corporate Medical Policy 2.02.44 Genetic Testing for Susceptibility to Hereditary Cancers for genetic testing for mutations in other high to moderate and low penetrance genes associated with other inherited cancers (e.g., ATM, BARD1, BRIP1, CDH1, CHEK2, NBN, PALB2, RAD50, and RAD51C) which are part of next generation sequencing panels (e.g., CancerNext™, OvaNext™, OncoGene Dx, and myRisk™ Hereditary Cancer).

Refer to Corporate Medical Policy #2.02.03 regarding Genetic Testing for Specific Diseases.

Refer to Corporate Medical Policy 2.02.06 Genetic Testing for Hereditary BRCA Mutations.

Refer to Corporate Medical Policy 2.02.44 Genetic Testing for Susceptibility to Hereditary Cancers.

Refer to Corporate Medical Policy #11.01.03 Experimental and Investigational Services.

Refer to Corporate Medical Policy #11.01.12 regarding Screening Tests.

POLICY GUIDELINES:

I. Supporting documentation required:
   The purpose of genetic testing is to provide information that will guide decisions regarding cancer prevention, surveillance, and treatment options. Documentation which must be submitted for review includes:
   A. Family history (pedigree) which includes first-, second-, and third-degree relatives, identifying family members affected with cancer; and
   B. Type of cancer, age at diagnosis for each affected (a personal history of) family member and whether they are living or deceased;
   C. Genetic testing results from any other family members. If family member(s) have not been tested (and are more appropriate to be tested first), clear and distinct rationale as to why the family member(s) cannot be tested (i.e., specific reason why testing was declined); and
   D. Documentation of discussion between the physician and member of rationale for genetic testing and treatment options for the individual patient based on test results; and
   E. Documentation of discussion between the physician and unaffected member of rationale for genetic testing when the affected family member cannot be tested including that a negative result for an unaffected individual with only a family history of cancer is considered indeterminate (or uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

II. It is recommended that, when possible, initial genetic testing be performed in an affected family member meeting clinical diagnostic criteria since an affected (personal history of cancer) individual has the highest likelihood for a positive test result. Subsequent testing in unaffected family members can then focus on the mutation found in the affected family member. A negative result for an unaffected (an individual who does not have cancer) individual with a family history only is considered indeterminate (uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

III. It is recommended that unaffected individuals with a strong family history who do not meet The Amsterdam II criteria be referred to an adequately trained health care professional (genetic counselor) to provide an appropriate genetic risk assessment to determine the individual’s risk for developing cancer.
IV. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.

V. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

DESCRIPTION:

Lynch syndrome (LS) or hereditary nonpolyposis colorectal cancer (HNPCC), MUTYH- associated polyposis, Familial adenomatous polyposis (FAP),and juvenile polyposis syndrome (JPS) are four forms of inherited colorectal cancer for which genetic testing is now available. Although they account only for an estimated 5-10% of all colorectal cancers, all of the syndromes have a high risk of colon cancer.

The optimal testing strategy is to define the specific genetic mutation in an affected family member and offer genetic counseling and testing of the unaffected family members to determine if they have inherited the same mutation. Identification of the at-risk family members helps guide the decision making about frequency of surveillance procedures and/or prophylactic treatment.

I. Familial adenomatous polyposis (FAP) and Attenuated Familial Adenomatous Polyposis (AFAP): Germ line alterations in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are inherited in an autosomal-dominant fashion and are responsible for FAP. The diagnosis is based on clinical findings of multiple colorectal adenomatous polyps (often in excess of 100) with onset as early as 10 years. An individual that is a FAP gene carrier has a near 100% lifetime risk of developing colon cancer. FAP accounts for 1% of all colorectal cancer cases and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina, referred to as Gardner’s syndrome. Other cancers are also sometimes observed in FAP including duodenal, thyroid, pancreatic, and hepatoblastoma malignancies. Once a diagnosis of FAP is made in a family, intensive surveillance is recommended for all at-risk relatives because of the high probability of carrying an APC gene mutation. AFAP, an attenuated variety of FAP, is characterized by fewer than 100 adenomatous polyps in the colorectum with proximal predominance and later onset (age 55). The most informative testing strategy requires an affected family member to be the first tested.

II. Lynch syndrome (LS) or hereditary nonpolyposis colorectal cancer (HNPCC): LS is associated with mutations in 1 of 4 different genes. These genes are known as MLH1, MSH2, MSH6, and PMS2. A fifth gene, known as EPCAM can have a germline mutation that inactivates MSH2. All of the genes are involved in DNA mismatch repair (MMR) mechanisms. The majority of HNPCC patients have mutations in either hMLH1 or hMSH2. As a result, sequencing for MMR gene mutations in suspected LS families is usually limited to MLH1 and MSH2 and, sometimes, MSH6. PMS2 gene testing can be considered if family history supports the phenotype seen in PMS2-Lynch families. A mutation in the EPCAM gene silences MSH2 and should be considered in genetic risk assessment. The gene size and the difficulty of detecting mutations in either of these genes make direct sequencing a time- and cost-consuming process. A LS gene carrier has an approximate 80% risk of colon cancer, mean age of onset is 44 years and the tumors are primarily right-sided. LS is estimated to account for 3% to 5% of colorectal cancer and is also associated with an increased risk of extra colonic cancer. Endometrial cancer is the sentinel cancer in women with an LS mutation who have an approximate 60% lifetime risk. Other extracolonic cancers in LS include ovarian, gastric, small bowel, biliary, urinary and sebaceous gland cancers.
III. Juvenile polyposis syndrome occurs in approximately one in every 100,000 persons. As in the other syndromes, it is inherited in an autosomal dominant fashion. It is clinically suspected when 3 to 10 juvenile polyps are found in the colon, or juvenile polyps are found outside the colon. Polyps are found most often in the colon but may occur throughout the GI tract. Malignancy arises from changes in the juvenile polyps. Patients with juvenile polyposis syndrome often have complications from the polyps early in life but have a colon cancer risk approaching 60% over a lifetime. Gastric, small intestinal, and pancreatic cancers also occur. Approximately 15% of juvenile polyposis syndrome patients are found to have mutations of the MADH4 gene, whereas 25% have mutations of the BMPR1A gene and possibly 5% from the PTEN gene.

IV. MUTYH-associated polyposis (MAP), is an autosomal recessive form of familial adenomatous polyposis. Mutations in the MUTYH gene affect the ability of cells to correct mistakes made during DNA replication. Both copies of the gene are mutated in individuals who have MUTYH-associated polyposis. These germline mutations in MUTYH predispose persons to multiple adenoma or polyposis coli. The phenotype is often indistinguishable from FAP although the number of adenomas is often lower. Generally the mean age at diagnosis is 48-56 years. The absolute risk of colorectal cancer is not known. A number of extracolonic manifestations have been observed, although their incidence is not yet well established. Similar to FAP, these include duodenal polyposis, duodenal cancer, osteomas, dental cysts and congenital hypertrophy of the retinal pigment epithelium. Breast cancer and thyroid cancer, and cutaneous tumors (pilomatricomas and sebaceous gland tumors) have also been reported.

V. Peutz-Jeghers syndrome (PJS) is an autosomal-dominant condition characterized by the association of gastrointestinal polyposis, mucocutaneous pigmentation, and cancer predisposition. Peutz-Jeghers-type hamartomatous polyps are most common in the small intestine (in order of prevalence: in the jejunum, ileum, and duodenum) but can also occur in the stomach, large bowel, and extraintestinal sites including the renal pelvis, bronchus, gall bladder, nasal passages, urinary bladder, and ureters. Gastrointestinal polyps can result in chronic bleeding and anemia and also cause recurrent obstruction and intussusception requiring repeated laparotomy and bowel resection. Mucocutaneous hyperpigmentation presents in childhood as dark blue to dark brown macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. Hyperpigmented macules on the fingers are common. The macules may fade in puberty and adulthood. Individuals with Peutz-Jeghers syndrome are at increased risk for a wide variety of epithelial malignancies (colorectal, gastric, pancreatic, breast, and ovarian cancers).

While FAP, MUTYH, and Juvenile Polyposis can be identified by appearance of characteristic colon polyps, the identification of HNPCC is based primarily on family history and related clinical criteria. The Amsterdam II Criteria is one such set of clinical criteria. The Revised Bethesda Guidelines provide clinical direction for the use of microsatellite instability (MSI) testing and IHC analysis to screen colon or endometrial cancer tumor slides to help determine whether the individual and family history may be linked to an LS mutation.

<table>
<thead>
<tr>
<th>Amsterdam II Criteria</th>
<th>Revised Bethesda Guidelines</th>
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<tbody>
<tr>
<td>The Amsterdam II Criteria (revised from the original to include extracolonic Lynch syndrome associated cancers) include ALL of the following:</td>
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<td>• 3 or more relatives with a histologically verified Lynch syndrome associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter or renal pelvis); AND</td>
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<td>• 1 of whom is a first-degree relative of the other 2; AND</td>
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<td>• HNPCC-associated cancer involving at least 2 generations; AND</td>
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<td>The Revised Bethesda Criteria for testing colorectal tumors or endometrial tumors include ANY of the following:</td>
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<td>• Individuals diagnosed with colorectal cancer before age 50; OR</td>
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SUBJECT: GENETIC TESTING FOR INHERITED SUSCEPTIBILITY TO COLORECTAL CANCER

POLICY NUMBER: 2.02.11
CATEGORY: Laboratory Test

EFFECTIVE DATE: 09/16/99
REVISED DATE: 04/19/01, 05/16/02, 06/19/03, 05/19/04, 06/16/05, 04/20/06, 04/19/07, 02/21/08, 05/24/12, 04/18/13, 07/17/14, 08/20/15, 08/18/16, 08/17/17
(ARCHIVED DATE: 12/18/08 EDITED DATE: 12/17/09, 01/20/11)

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- Cancer in one or more affected relatives diagnosed before 50 years of age; AND
- Familial adenomatous polyposis excluded in any cases of colorectal cancer.

Modifications allow for small Lynch syndrome families: these families must have two colorectal cancers in first-degree relatives involving at least 2 generations, with at least one individual diagnosed by age 55.

- Individuals with colorectal cancer with the MSI-H histology diagnosed in a patient less than age 60; OR
- Individuals with colorectal cancer and 1 or more first-degree relatives with colorectal cancer and/or Lynch syndrome-related cancer*; with 1 of the cancers was diagnosed at age less than 50 years; OR
- Individuals with colorectal cancer and colorectal cancer diagnosed in 2 or more first- or second-degree relatives with Lynch syndrome-related tumors* regardless of age.

*LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers as well as sebaceous gland adenomas and keratocanthonas as seen in Muir-Torre syndrome.

Serum genetic testing for LS is normally done to detect a mutation in one of the MMR genes, MLH1, MSH2, MSH6 and PMS2. Approximately a 1-3% of LS families are linked to a mutation in EPCAM. These families may meet the Amsterdam II criteria but test negative for MLH1, MSH2, MSH6 and PMS2. Microsatellite instability (MSI) and Immunohistochemical (IHC) analysis are two tests performed on colorectal or endometrial cancer tumor tissue to identify individuals who may have LS. The sensitivities of MSI and IHC testing are estimated to be 77-89% and 83%, respectively while specificities are estimated to be 90% and 89%, respectively. MSI tumor DNA testing is divided into MSI-high and MSI-low categories. MSI-high in tumors refers to changes in two or more of the five microsatellite markers in the National Cancer Institute-recommended panel. MSI testing may be performed initially followed by IHC or further testing for mutations in MLH1, MSH2 and MSH6 genes; if the tumor tissue is found to be MSI-high. For tumors which test MSI-low or microsatellite stable tumors, mutations in MSH6 or PMS2 are less likely but may be still possible. Further testing may depend on the individual risk based on family history. Immunohistochemical (IHC) analysis of tumor tissue refers to staining tumors tissue for protein expression of the four mismatch genes know to be mutated in LS: MLH1, MSH2, MSH6, and PMS2. A normal IHC test implies all four mismatch repair proteins are normally expressed and no underlying mismatch repair gene mutation is present in the related gene. Loss of protein expression in any one of the mismatch repair genes by IHC guides genetic testing or mutation detection to the gene where the protein expression is not observed. Consequently IHC analysis is advantageous in that it can predict which gene is most likely mutated and should be tested for first. Since there is a 5-10% false negative-rate for MSI and IHC testing, the tests are not a prerequisite for each screening test for inherited susceptibility to colorectal or endometrial cancer. Family and personal history and a clinical evaluation should be utilized in the decision making process of which test should be initially performed.

RATIONALE:

The American Society of Clinical Oncology recommends that genetic testing be considered when:
I. the individual has personal or family history features suggestive of a genetic cancer susceptibility condition,
II. the test can be adequately interpreted, and
III. the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.
Evidence from published literature and BCBS TEC Assessment indicates that genetic testing for familial adenomatous polyposis (FAP) may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy. At-risk subjects are considered to be those with greater than 20 colon polyps or first-degree relatives of patients with known FAP. The optimal testing strategy is to define the specific genetic mutation in an affected family member and then test the unaffected family members to see if they have inherited the same mutation.

Evidence from peer-reviewed literature and consensus from specialty organizations such as the American Gastroenterological Association and the National Cancer Institutes indicate that genetic testing for LS mutations in affected patients is appropriate for individuals who meet either the Amsterdam II Criteria or Revised Bethesda guidelines. Genetic testing of unaffected individuals is generally considered appropriate in those patients who have a first- or second-degree relative with a known LS mutation. There is good evidence indicating that testing in these individuals may improve health outcomes. Clinical benefits include identifying patients who will require increased surveillance, determining best surveillance methods, and suggesting prophylactic, surgical options.

The American College of Gastroenterology (2015) recommends that all newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency. Analysis may be done by immunohistochemical testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability (MSI). Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation. Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF mutation or hypermethylation of MLH1) a known family mutation associated with LS, or a risk of 5% or greater chance of LS based on risk prediction models should undergo genetic evaluation for LS.

The US Multi-Society Task Force on Colorectal Cancer (2014) developed guidelines to assist health care providers with the appropriate provision of genetic testing and management of patients at risk for and affected with Lynch syndrome. Testing for MMR deficiency of newly diagnosed CRC should be performed. This can be done for all CRCs, or CRC diagnosed at age 70 years or younger, and in individuals older than 70 years who have a family history for LS. Analysis can be done by IHC testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for MSI. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (2015) endorsement of the familial risk – colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines recommend tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines. If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated. If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1). Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis.

Sufficient evidence exists to support confirmatory and predisposition genetic testing for juvenile polyposis syndrome. JPS is inherited in an autosomal dominant manner. Two genes are known to be associated with JPS:

I. BMPR1A. About 20% of individuals affected with JPS have mutations in the BMPR1A gene

II. SMAD4. Approximately 20% of individuals affected with JPS have mutations in the SMAD4 gene

In individuals meeting the diagnostic criteria for JPS, genetic testing can be performed to help confirm the clinical diagnosis of JPS. Genetic testing to identify at-risk family members helps guide the decision making about frequency of surveillance procedures and/or prophylactic treatment. Approximately 75% of individuals with JPS have an affected
**SUBJECT:** GENETIC TESTING FOR INHERITED SUSCEPTIBILITY TO COLORECTAL CANCER

**POLICY NUMBER:** 2.02.11  
**CATEGORY:** Laboratory Test

| EFFECTIVE DATE: 09/16/99  
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| (ARCHIVED DATE: 12/18/08)  
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Parent. The risk to the siblings of a proband depends upon the genetic status of the proband's parents. If a parent of the proband has the disease-causing mutation the risk to the siblings is 50%. If molecular genetic testing and/or surveillance measures have demonstrated that the parents are not likely to be affected, then the risk to the siblings would be negligible. Each child of an affected individual has a 50% chance of inheriting the mutation and developing JPS. The risk to other family members depends on the status of the proband's parents. If a parent is affected, then his/her relatives are also at risk and may benefit from molecular genetic testing and/or surveillance. (Haidle JL, et al.)

**MUTYH-associated polyposis** is a recently described syndrome. The National Comprehensive Cancer Network (NCCN) 2015 practice guidelines on colorectal cancer screening recommends testing for MUTYH mutations for individuals with a personal history of adenomatous polyposis (more than 20 adenomas with negative adenomatous polyposis coli [APC] mutation testing). The guideline noted that when polyposis is present in a single person with negative family history, de novo APC mutation should be tested; if negative, testing for MUTYH should follow. When family history is positive only for a sibling, recessive inheritance should be considered and MUTYH testing should be done first. The absolute risk of colorectal cancer and the role of surgery in patients with MUTYH is not clearly established. Periodic colonoscopy of the entire colon should be considered for biallelic mutations carriers. Prophylactic colectomy may be considered when the number, size and/or dysplasia of the polyps make continued surveillance unmanageable. Upper gastrointestinal surveillance is also indicated. Parents and children of individuals with biallelic mutations are obligate carriers of at least one MUTYH mutation. A baseline colonoscopy has been suggested for these carriers, and, if findings are negative, screening should be repeated every 3-5 years.

The diagnosis of Peutz-Jeghers syndrome (PJS) is based on the constellation of family history, mucocutaneous macules, PJS-type intestinal polyps, and presence of a disease-causing mutation in STK11. Individuals with PJS also develop many other polyps; polyps showing adenomatous changes frequently arise in the colon and may cause confusion with familial adenomatous polyposis. The histology of gastric PJS polyps can be similar to gastric hyperplastic polyps. Protocols have been suggested for monitoring stomach, small and large bowel, breasts, testicles, ovaries, uterus, and pancreas by various procedures as early as birth and as frequently as once a year.

A review of the literature reporting on MSI testing among patients selected for increased risk of LS using Amsterdam, Bethesda, or similar criteria suggests that MSI testing could be considered medically necessary to identify those patients with colon cancer who meet such criteria to identify those most likely to benefit from HNPCC genetic testing. Microsatellite instability has been found in 90% of LS HNPCC. Testing for hMSH2 and hMLH1 in patients with MSI-high mutations, can both identify those patients who definitively have MMR mutation(s) and should proceed with LS testing, and rule out any need for further genetic testing for patients who are MSI-negative or MSI-low. The National Comprehensive Cancer Network (NCCN) 2014 Guidelines for Colorectal Cancer Screening suggests that MSI testing is performed at some centers on all patients with colorectal cancers and endometrial cancers regardless of age or family history to identify individuals at risk for Lynch syndrome. NCCN goes on to state that the cost effectiveness of this approach has been confirmed for colorectal cancer and endorsed by the Evaluation of Genomic Applications in Prevent and Practice (EGAPP) working group. In addition, EGAPP has endorsed IHC and/or MSI screening of all endometrial cancers regardless of age at diagnosis or family history.

Other cancers that occur with increased frequency in persons affected with the LS mutation include gastric, ovarian, pancreas, urethral, brain (glioblastoma), and small intestinal cancers.

Absent or reduced protein expression may be a consequence of an MMR gene mutation. Immunohistochemistry (IHC) assays for the expression of MLH1, MSH2, MLH6 and PMS2 can be used to detect loss of expression of these genes and to focus LS mutation testing efforts on a single gene. It is also possible for IHC assays to show loss of expression, thus indicating the presence of a mutation, when LS mutation testing is negative for a mutation. In such cases, mutations may be in regulatory elements that cannot be detected. IHC technology is readily available in many clinical laboratories. A result of MSI-H and no loss of MLH1 or MSH2 expression by IHC could indicate a mutation in EPCAM. MSI-H and loss of expression of MLH1 may also indicate a sporadic cancer if a V600E mutation is present in the BRAF gene or

*Proprietary Information of Excellus Health Plan, Inc.*
that there has been a methylation of the promoter region of MLH1. Thus, although the results of MSI and IHC testing are usually overlapping, in some cases they may provide complementary information. MSI and IHC testing are both linked.

### Codes

Eligibility for reimbursement is based upon the benefits set forth in the member’s subscriber contract.

**Codes may not be covered under all circumstances. Please read the policy and guidelines statements carefully.**

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

#### CPT:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81210</td>
<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutl homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
</tr>
<tr>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81293</td>
<td>MLH1 (mutl homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81294</td>
<td>MLH1 (mutl homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81295</td>
<td>MSH2 (muts homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81296</td>
<td>MSH2 (muts homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81297</td>
<td>MSH2 (muts homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81298</td>
<td>MSH6 (muts homolog 6 [e. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
</tbody>
</table>
81299 MSH6 (muts homolog 6 [e. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300 MSH6 (muts homolog 6 [e. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301 Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81317 PMS2 (postmeiotic segregation increased 2 [S. Cerveisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318 PMS2 (postmeiotic segregation increased 2 [S. Cerveisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319 PMS2 (postmeiotic segregation increased 2 [S. Cerveisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81435 (E/I) Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatos polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436 (E/I) Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatos polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

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HCPCS: No specific code(s)

ICD9:

153.0-153.9 Malignant neoplasm of the colon, code range
154.0 Malignant neoplasm of the rectosigmoid junction
211.3 Benign neoplasm of the colon
211.4 Benign neoplasm of the rectum and anal canal
230.3 Carcinoma in situ of the colon
230.4 Carcinoma in situ of the rectosigmoid junction
235.2 Neoplasm of uncertain behavior of digestive system; stomach, intestines and rectum
239.0-239.7 Neoplasm of unspecified nature; digestive system
V10.05 Personal history of malignant neoplasm; large intestine

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V10.06 Personal history of malignant neoplasm; rectum, rectosigmoid junction, and anus
V16.0 Family history of malignant neoplasm; gastrointestinal tract
V26.31-V26.39 Genetic counseling and testing

**ICD10:**

C18.0-C18.9 Malignant neoplasm of colon (code range)
C19 Malignant neoplasm of rectosigmoid junction
D01.0-D01.2 Carcinoma in situ of other and unspecified digestive organs (code range)
D12.0-D12.6 Benign neoplasm of colon, rectum, anus and anal canal (code range)
D37.1-D37.5 Neoplasm of uncertain behavior of digestive organs (code range)
D49.0 Neoplasm of unspecified behavior of digestive system
K63.5 Polyp of colon
Z31.430-Z31.448 Encounter for genetic testing of female or male for procreative management (code range)
Z31.5 Encounter for genetic counseling
Z80.0 Family history of malignant neoplasm of digestive organs
Z85.038 Personal history of other malignant neoplasm of large intestine
Z85.048 Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus

**REFERENCES:**


*BlueCross BlueShield Association Technical Evaluation Center. Genetic testing for inherited susceptibility to colorectal cancer part-I adenomatous polyposis coli gene mutations. 1998 Jun;3(10).

*BlueCross BlueShield Association Technical Evaluation Center. Genetic testing for inherited susceptibility to colorectal cancer part-II hereditary nonpolyposis colorectal cancer. 1998 Jun;13(11).


*Proprietary Information of Excellus Health Plan, Inc.*
SUBJECT: GENETIC TESTING FOR INHERITED SUSCEPTIBILITY TO COLORECTAL CANCER

POLICY NUMBER: 2.02.11
CATEGORY: Laboratory Test

EFFECTIVE DATE: 09/16/99
REVISED DATE: 04/19/01, 05/16/02, 06/19/03, 05/19/04, 06/16/05, 04/20/06, 04/19/07, 02/21/08, 05/24/12, 04/18/13, 07/17/14, 08/20/15, 08/18/16, 08/17/17
(ARCHIVED DATE: 12/18/08 EDITED DATE: 12/17/09, 01/20/11)
PAGE: 14 OF 14


*key article

KEY WORDS:
COLARIS®, Colon cancer, familial adenomatous polyposis (FAP), Genetic testing, hereditary nonpolyposis colorectal cancer (HNPCC), juvenile polyposis syndrome (JPS), Microsatellite instability (MSI), MYH-associated polyposis (MAP)

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**CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS**


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