Medical Policy

Genetic Testing for Hereditary Colorectal Cancer

Policy Number: OCA 3.64
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Product Applicability

- All Plan+ Products

Well Sense Health Plan
- New Hampshire Medicaid
- NH Health Protection Program

Boston Medical Center HealthNet Plan
- MassHealth
- Qualified Health Plans/ConnectorCare/Employer Choice Direct
- Senior Care Options ◊

Notes:
+ Disclaimer and audit information is located at the end of this document.
◊ The guidelines included in this Plan policy are applicable to members enrolled in Senior Care Options only if there are no criteria established for the specified service in a Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) on the date of the prior authorization request. Review the member’s product-specific benefit documents at www.SeniorsGetMore.org to determine coverage guidelines for Senior Care Options.

Policy Summary

The Plan considers genetic mutation testing for hereditary colorectal cancer to be medically necessary for a member (regardless of gender) when the Plan’s medical criteria are met. Prior authorization is required for all genetic testing. Fecal DNA testing for colorectal cancer is considered experimental and investigational. Plan prior authorization is required for all molecular and chromosomal genetic testing.

The Plan supports the National Comprehensive Cancer Network (NCCN) guidelines for genetic counseling for all genetic tests conducted with Plan members; NCCN recommends that adequate pre-test and post-test genetic counseling be provided by a health care professional with expertise in

Genetic Testing for Hereditary Colorectal Cancer

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Genetic counseling provided to a Plan member (and/or guardian if the member is under the age of 18) should be documented in the member’s medical record and conducted by an appropriately trained practitioner with expertise and experience in genetics, including a provider acting within the scope of the practitioner’s license and practice, clinical geneticist, or genetic counselor.

It will be determined during the Plan’s prior authorization process if the testing is considered medically necessary for the requested indication. See the Plan’s policy, *Medically Necessary* (policy number OCA 3.14), for the product-specific definitions of medically necessary treatment. Refer to the Plan’s policy, *Experimental and Investigational Treatment* (policy number OCA 3.12), for the product-specific definitions of experimental or investigational treatment.

See the following Plan medical policies for additional prior authorization guidelines for genetic testing available at [www.bmchp.org](http://www.bmchp.org) for BMC HealthNet Plan members (or at [www.SeniorsGetMore.org](http://www.SeniorsGetMore.org) for Senior Care Options members) and [www.wellsense.org](http://www.wellsense.org) for Well Sense Health Plan members:

1. *Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies*, policy number OCA 3.573
2. *Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests)*, policy number OCA 3.572
3. *Genetic Testing for Familial Malignant Melanoma*, policy number OCA 3.78
5. *Genetic Testing Guidelines and Pharmacogenetics*, policy number OCA 3.727
7. *Genetic Testing for Hereditary Thrombophilia*, policy number OCA 3.728
8. *Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening)*, policy number OCA 3.726

**Description of Item or Service**

**Genetic Blood Tests, Saliva Tests, or Buccal Swabs for Hereditary Colorectal Cancer:** A sample is tested to check for specific changes (mutations) in genes that help control normal cell growth, including the APC, EPCAM, MLH1, MSH2, MSH6, and PMS2 genes, to determine if an individual has an increased susceptibility to Lynch syndrome (or hereditary nonpolyposis colorectal cancer, HNPCC), familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), or mutY homolog (MUTYH)-associated polyposis (MAP).
**Genetic Tumor Tissue Tests for Hereditary Colorectal Cancer:** Tissue specimens of colorectal cancer are analyzed to identify specific gene mutations, diagnosis a hereditary colorectal cancer syndrome (e.g., Lynch syndrome), and customize the individual’s care management strategy based on the diagnosis.

**Medical Policy Statement**

The Plan considers genetic testing for hereditary colorectal cancer to be medically necessary when the following applicable medical criteria are met and documented in the member’s medical record. The criteria are categorized into the following two (2) major sections: Section I for genetic testing for hereditary polyposis syndromes (e.g., attenuated familial adenomatous polyposis [AFAP], familial adenomatous polyposis [FAP], and/or mutY homolog [MUTYH]-associated polyposis [MAP]); and Section II for genetic testing for hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome). See the Definitions section of this Plan policy.

I. Genetic Testing for Hereditary Polyposis Syndromes:

It is important to distinguish among classical FAP, attenuated FAP, and MAP by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome. (See the Definitions section of this Plan policy.) Applicable Plan criteria must be met for genetic testing for the following conditions, as specified below in item A (for FAP or AFAP) or item B (for MAP).

A. APC Gene Mutation Testing Associated with Familial Adenomatous Polyposis (FAP) or Attenuated Familial Adenomatous Polyposis (AFAP):

FAP and AFAP are due to mutations in the adenomatous polyposis coli (APC) gene. The APC gene is a tumor suppressor gene which regulates cellular growth and proliferation. BOTH of the following applicable criteria must be met for the evaluation of APC gene mutations associated with FAP and/or AFAP, as specified below in item 1 and item 2:

1. The test results will be used to make a clinical management decision; AND

2. At least ONE (1) of the following medical criteria is met for APC genetic testing, as specified below in items a through f:
   a. Member has a personal history of 10 or more adenomas (adenomatous polyps); OR
   b. Member has a personal history of desmoid tumor; OR
   c. Member has a personal history of hepatoblastoma; OR
d. Member has a personal history of cribriform-morular variant of papillary thyroid cancer; OR

e. For predictive testing in a member age 10 or older who is a first-degree relative of an affected individual and/or proband with a disease causing mutation for FAP or AFAP and/or a known APC mutation; OR

f. Member has a differential diagnosis of AFAP vs. MAP vs. Lynch syndrome (with the order of testing for APC mutations or MMR mutations determined by clinical presentation, as determined by the treating specialist).

B. MUTYH Gene Mutation Testing Associated with MUTYH-Associated Polyposis (MAP):

MUTYH-associated polyposis (MAP) is caused by mutations in the MUTYH gene. BOTH of the following applicable criteria must be met for the evaluation of MUTYH gene mutations associated with MAP, as specified below in item 1 and item 2:

1. The test results will be used to make a clinical management decision; AND

2. At least ONE (1) of the following medical criteria is met, as specified below in items a through c:

   a. For confirmatory testing in individuals with a personal history of adenomatous polyposis (more than 10 adenomas); OR

   (Note: According to NCCN guidelines, MUTYH genetic testing is NOT indicated for a personal history of a desmoid tumor, hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer. When APC mutation testing is negative, MUTYH genetic testing may be medically necessary when applicable Plan criteria are met. The order of testing for APC and MUTYH genetic testing is at the discretion of the treating provider.)

   b. Findings are consistent with recessive inheritance with an at-risk family member with a known deleterious MUTYH mutation (with an at-risk family member defined as a first-degree relative of the member, including a full biological sibling and/or proband); OR

   c. The member has a personal history of serrated polyposis syndrome meets at least ONE (1) of the following criteria, as specified below in item (1) or item (2):

               (1) Personal history of at least five (5) serrated polyps (which may include hyperplastic polyps, sessile serrated adenomas/polyps, and/or traditional serrated adenomas) proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; OR
(2) Personal history of some adenomas with greater than 20 serrated polyps (which may include hyperplastic polyps, sessile serrated adenomas/polyps, and/or traditional serrated adenomas) of any size distributed throughout the colon (excluding polyps localized to the rectum and sigmoid unless those polyps are greater than 10 mm or serrations extend beyond widened base).

II. Genetic Testing for Hereditary Nonpolyposis Colorectal Cancer (HNPCC or Lynch Syndrome):

Lynch syndrome is associated with a mutation in one (1) of the mismatch repair mechanism (MMR) genes (i.e., MLH1, MSH2, MSH6, or PMS2). Recent evidence has shown that three (3) deletions in the EPCAM gene are an additional cause of Lynch syndrome. The following applicable criteria must be met for genetic testing for Lynch syndrome/HNPCC, as specified below in item A for testing for mismatch repair mechanism (MMR) gene mutation, item B for tissue specimen sampling with immunohistochemistry (IHC) and/or microsatellite instability (MSI), and/or item C for EPCAM gene mutation testing:

A. Evaluation of Mismatch Repair (MMR) Mechanism Gene Mutation to Diagnose Lynch Syndrome (e.g., Blood Test for Gene Mutation of MLH1, MSH2, MSH6, and/or PMS2 Genes):

BOTH of the following criteria must be met, as specified below in item 1 and item 2:

1. The test results will be used to make a clinical management decision; AND

2. At least ONE (1) of the following medical criteria is met, as specified below in items a through e:
   
   a. Endometrial cancer is diagnosed before age 50 (for the diagnosis of Lynch syndrome); OR

   b. Colorectal cancer diagnosed ≤ age 70 (for the diagnosis of Lynch syndrome); OR

   c. EITHER the Amsterdam II criteria or the Revised Bethesda guidelines are met, as specified below in item (1) or item (2):

   (1) Amsterdam II Criteria:

   Member is age 18 or older with three (3) or more relatives with a histologically verified HNPCC-associated cancer** (see note) and ALL of the following criteria must be present, as specified below in items (a) through (e):

   (a) One (1) relative must be a first-degree relative of the other two (2); AND
(b) At least two (2) successive generations must be affected; AND

(c) At least one (1) of the relatives with HNPCC-associated cancer\(^*\) (see note) should be diagnosed before 50 years of age; AND

(d) FAP should be excluded in the colorectal cancer cases (if any); AND

(e) Tumors should be verified by pathological examination whenever possible; OR

(2) Revised Bethesda Guidelines:

Individual must meet at least ONE (1) of the following criteria, as specified below in items (a) through (e):

(a) Individual diagnosed with colorectal cancer < 70 years of age; OR

(b) Individual with HNPCC-related cancer\(^*\) (see note), including synchronous and metachronous colorectal cancers or associated extracolonic cancers, regardless of age; OR

(c) Individual diagnosed at any age with colorectal cancer with the microsatellite instability-high (MSI-H) tumor histology; OR

(d) Individual with colorectal cancer at any age and one (1) or more first-degree relatives with colorectal cancer and/or HNPCC-related extracolonic cancer\(^*\) (see note) diagnosed before 50 years of age; OR

(e) Individual with colorectal cancer at any age and colorectal cancer diagnosed in two (2) or more first- or second-degree relatives with HNPCC-related\(^*\) (see note) tumors at any age; OR

d. For predictive testing in a member age 18 or older who meets at least ONE (1) of the following criteria, as specified below in item (1) or item (2):

(1) A first-degree relative or second-degree relative of an individual satisfying the Amsterdam II criteria or Revised Bethesda guidelines (as specified above); OR

(2) A first-degree or second-degree relative of an individual with a known MMR mutation for Lynch syndrome; OR
e. Member has a differential diagnosis of AFAP vs. MAP vs. Lynch syndrome (with the order of testing for APC mutations or MMR mutations determined by clinical presentation, as determined by the treating specialist)

B. Genetic Testing of Colorectal Cancer Tissue for the Diagnosis of Lynch Syndrome Using Immunohistochemistry (IHC) and/or Microsatellite Instability (MSI):

Genetic testing of colorectal cancer tumor tissue from a member using IHC and/or MSI (e.g., BRAF mutation analysis, Lynch syndrome MSI, and/or IHC for MLH1, MSH2, MSH6, and PMS2 genes) is considered medically necessary when at least ONE (1) of the following criteria is met, as specified below in items 1 through 5:

1. Endometrial cancer diagnosed in a patient < 50 years of age or colorectal cancer diagnosed < 70 years of age; OR

2. Presence of synchronous, or metachronous, colorectal or other Lynch syndrome-related tumors,** (see note) regardless of age; OR

3. Colorectal cancer with microsatellite instability-high (MSI-H) diagnosed in a patient at any age (with MSI-H demonstrating the presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern); OR

4. Colorectal cancer diagnosed in a patient with one (1) or more first-degree relatives with an Lynch syndrome-related cancer,** (see note) with one (1) of the cancers diagnosed under age 50 years; OR

5. Colorectal cancer diagnosed in a patient with two (2) or more first-degree or second-degree relatives with Lynch syndrome-related cancers,** (see note) regardless of age.

** Note: Lynch syndrome-related cancers/tumors 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 keratoacanthomas as seen in Muir-Torre syndrome.

C. EPCAM Gene Mutation Testing to Diagnose Lynch Syndrome:

For EPCAM gene mutation testing, BOTH of the following criteria must be met, as specified below in item 1 and item 2:

1. The test results will be used to make a clinical management decision; AND
2. At least ONE (1) of the following medical criteria is met, as specified below in item a, item b, or item c:

   a. Patients with colorectal cancer, for the diagnosis of Lynch syndrome, when at least ONE (1) of the following criteria are met, as specified below in item (1) or item (2):

      (1) Tumor tissue shows lack of MSH2 expression by immunohistochemistry (IHC) and member is negative for a germ line mutation in MSH2; OR

      (2) Tumor tissue with the microsatellite instability-high (MSI-H) histology and the member is negative for a germ line mutation in MLH1, MSH2, MSH6, and PMS2 genes; OR

      (3) The treating provider will conduct testing of all four (4) MMR genes (i.e., MLH1, MSH2, MSH6, and PMS2 genes) and EPCAM gene concurrently (RATHER than sequentially); OR

   b. At-risk relative (who is a member age 18 or older) of an individual with Lynch syndrome with a known EPCAM mutation; OR

   c. Member age 18 or older without colorectal cancer but with a family history meeting the Amsterdam II criteria or Revised Bethesda guidelines, when no affected family members have been tested for mismatch repair mechanism (MMR) mutations, and when sequencing for MMR mutations is negative.

Limitations

1. Fecal DNA testing for colorectal cancer is considered experimental and investigational for all BMC HealthNet Plan members (except Senior Care Options members) and Well Sense Health Plan members; an example of testing includes but is not limited to Cologuard™ by Exact Sciences Corp. Cologuard™ is covered for Senior Care Options members only according to the criteria specified in the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3) available at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=281&ncdver=5&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=colorectal+cancer&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAABAAAAAAA%3d%3d&

2. Genetic testing that is marketed directly to consumers (direct-to-consumer or DTC) that are ordered by a member without the order of a treating health care provider is not covered.
3. Plan Medical Director review is required for multigene panel testing as an alternative to, or in addition to, targeted genetic testing to predict susceptibility to hereditary colorectal cancer. Examples include but are not limited to the following: CancerNext Next-Gen Cancer Panel, ColoNext, High/Moderate Risk Panel by GeneDx Inc., iGene Cancer Panel, and Preventest).

The use of a multigene testing panel is generally considered to NOT be medically necessary as an alternative to or in addition to disease-specific genetic testing due to insufficient data on clinical validity and clinical utility of multigene testing. If the treating provider is recommending multigene panel testing rather than or in addition to the condition-targeted genetic testing, Plan Medical Director review is required. ALL of the following written documentation must be submitted to the Plan with the prior authorization request to determine the medical necessity of multigene panel testing, as specified below in items a through c:

a. A recommendation for multigene panel testing for the member by an independent Board-Certified or Board-Eligible Medical Geneticist, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory, or a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory; this provider has a documented evaluation of the member which includes a completed 3-generation pedigree and intends to engage in post-test follow-up counseling; AND

b. Member meets criteria for genetic testing outlined in the Medical Policy Statement section of this policy; AND

c. All genes included in the multigene panel are relevant to the personal history, family history, or treatment plan for the member being tested and there are professional society management guidelines or National Comprehensive National Comprehensive Cancer Network (NCCN) guidelines (with applicable references provided) documenting the clinical utility of testing for the members who test positive for any and all genes in the panel.

If ALL of the above criteria are not met (as specified in items a through c, the Plan considers the multigene panel testing to NOT be medically necessary; disease-targeted genetic testing is considered medically necessary as an alternative when Plan criteria are met in the Medical Policy Statement and Limitations sections specified in this policy. See the limitations section of Genetic Testing Guidelines and Pharmacogenetics policy, policy number OCA 3.727, for guidelines related to multigene panel testing to determine response to drug metabolism and adjuvant therapy.

Refer to the Plan policy, Medically Necessary (policy number OCA 3.14), for the product-specific definitions of medically necessary treatment. See Plan policy, Experimental and Investigational Treatment (policy number OCA 3.12), for the product-specific definitions of experimental or

Genetic Testing for Hereditary Colorectal Cancer

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investigational treatment. Review Plan policy, *Genetic Testing Guidelines and Pharmacogenetics*, policy number OCA 3.727, for Plan guidelines for genetic testing indications that may not be included in this Plan policy, including whole exome sequencing and whole genome sequencing.

**Definitions**

**Adenomatous Polyp:** An area where normal cells that line the inside of a person’s colon begin to make mucous and form a mass on the inside of the intestinal tract.

**Attenuated Familial Adenomatous Polyposis (AFAP):** Type of polyposis syndrome caused by an autosomal dominant trait that carries a high risk for the development of colorectal cancer. The condition is characterized by fewer adenomatous polyps in the colon and rectum than in classic familial adenomatous polyposis (FAP). AFAP is a variant (subtype) of FAP, but AFAP has fewer than 100 adenomatous colorectal polyps (with 30 being the average) and generally has a later age of onset than FAP (i.e., 55 years of age or older, although polyps may develop as early as the late teens). Both AFAP and FAP are associated with genetic mutations of the adenomatous polyposis coli or APC gene (normally a tumor suppressor gene) on chromosome 5q21. (See the definition for familial adenomatous polyposis [FAP].)

**Autosomal Dominant Trait:** Autosomal dominant inheritance means that the affected individual is genetically heterozygous (i.e., having dissimilar pairs of genes for any hereditary characteristic), such that each offspring of the affected individual has a 50% chance of inheriting the disease gene. A single, abnormal gene on one of the first 22 non-sex chromosomes from either parent can cause an autosomal disorder. Dominant inheritance means an abnormal gene from one parent can cause disease, even though the matching gene from the other parent is normal. The abnormal gene dominates. Each child’s risk is independent of whether their sibling has the disorder or not; children who do not inherit the abnormal gene will not develop or pass on the disease.

**Autosomal Recessive Trait/Recessive Inheritance:** A gene mutation that must be inherited from both biological parents in order for an individual to be affected with the disease or trait. The individual has received two (2) copies of the mutated gene (since genes come in pairs), one from each parent. Such parents are usually unaffected carriers because they only have a single copy of the abnormal gene. The individual who inherits two (2) copies of the same mutated gene is called a homozygote (i.e., a person who has two identical forms of a particular gene which may result in a genetic disorder, one gene is inherited from each parent); in this case, the individual’s parents, each with a single copy of the mutated gene, appear normal and are called gene carriers or heterozygotes (i.e., individuals who have two [2] different forms of a particular gene). The siblings of a patient with an autosomal recessive disease have, on average, a 25% chance of being affected with the same disease and a 50% chance of being carriers.

**Desmoid Tumors:** Proliferative, locally invasive, non-metastasizing, fibromatous tumors. Although they do not metastasize, they can grow very aggressively and be life threatening. Desmoids may occur sporadically, as part of classical FAP, or in a hereditary manner without the colon findings of familial

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adenomatous polyposis (FAP). Desmoids have been associated with hereditary APC gene mutations even when not associated with typical adenomatous polyposis of the colon.

**Familial Adenomatous Polyposis (FAP or Classical FAP):** A type of hereditary polyposis syndrome caused by an autosomal dominant trait that carries a high risk for the development of colorectal cancer. The condition is characterized by a young age of onset (mid-teens, age 12-15 years old). The individual develops multiple (> 100) adenomatous colon polyps that carry a high risk for the development of colorectal cancer. More than 95% of people with FAP will have multiple colon polyps by age 35. If FAP is not recognized and treated, there is almost a 100% chance that a person will develop colorectal cancer; the risk of colon cancer is 87% by age 45. Classic FAP is one of the most clearly defined and well understood of the inherited colon cancer syndromes, equally affecting all genders. Both AFAP and FAP are associated with genetic mutations of the adenomatous polyposis coli or APC gene (normally a tumor suppressor gene) on chromosome 5q21. Approximately 20% to 30% of FAP cases are caused by new mutations, meaning that an APC germline mutations may be present in an individual even if it is absent in both parents. (See the definition for attenuated familial adenomatous polyposis [AFAP].)

**Fecal DNA Testing for Colorectal Cancer:** Fecal DNA screening is a test that detects genetic alterations in the DNA from shed colorectal cancer cells isolated from stool samples that are submitted to a laboratory after being collected by patients at home or at an outpatient clinic. Aberrant cells are shed from precancerous or cancerous lesions in the colon and rectum into the feces and DNA from the aberrant cells can be extracted for mutation testing. At the present time the accuracy of fecal DNA testing is unknown. There are commercial fecal DNA tests for colorectal cancer that include the following:

1. **PreGen-26 assay (EXACT Sciences Corporation, Maynard, MA):** The PreGen-26 detects a mutation in the gene Big A-Tr act (BAT-26), a marker that has been associated with HNPCC.

2. **PreGen-Plus (EXACT Sciences Corporation, Maynard, MA):** The PreGen-Plus is a single test that identifies 23 different mutations in genes associated with colorectal cancer.

**First Degree Relative:** A blood relative of an individual who shares approximately 50% of the individual’s genes defined as a biological parent, full sibling, or biological child.

**Genetic Testing:** According to U.S. Library of Medicine, genetic testing is defined as a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder. More than 1,000 genetic tests are currently in use, and more are being developed. Several methods can be used for genetic testing:

1. Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.

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Genetic Testing for Hereditary Colorectal Cancer

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2. Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.

3. Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

**Hereditary Polyposis Syndrome/Hereditary Mixed Polyposis Syndrome:** A genetic condition that is associated with an increased risk of developing polyps (cancerous and/or noncancerous) in the digestive tract. Examples of hereditary polyposis syndromes that are associated with increased risk of hereditary colorectal cancer include attenuated familial adenomatous polyposis (AFAP), familial adenomatous polyposis (FAP), and MYH-associated polyposis (MAP).

**Immunohistochemistry (IHC):** IHC testing uses special dyes to stain tissue samples. The presence or absence of staining indicates whether certain proteins are present in the tissue and identify which mutated genes caused the cancer. (This is one of the two main initial tests performed on colorectal cancer tissue specimens to identify individuals who might have Lynch syndrome.)

**Lynch Syndrome or Hereditary Nonpolyposis Colorectal Cancer (HNPCC):** Lynch syndrome (also known as HNPCC) this is the most common form of hereditary colorectal cancer caused by an autosomal dominant trait, accounting for 2% to 4% of all colorectal cancer cases. Lynch syndrome is associated with a mutation in one of the mismatch repair mechanism (MMR) genes (i.e., MLH1, MSH2, MSH6, or PMS2). Recent evidence has shown that three deletions in the EPCAM gene are an additional cause of Lynch syndrome. Individuals with MLH1 and MSH2 gene mutations are often diagnosed with Lynch syndrome before age 50. Individuals with mutation of the MSH6 gene may have colorectal cancer diagnosed later in life, or over age 50. Other possible associated genetic mutations with Lynch syndrome may be with the MLH3, PMS1, and EXO1 genes.

**Microsatellite Instability (MSI):** MSI is a genetic marker found in colorectal cancers as a result of the inactivation of the DNA mismatch repair (MMR) system. With Lynch syndrome, the individual has inherited a mutated copy of a DNA repair gene. If the remaining non-mutated copy of that DNA repair gene is deactivated in any cell, that cell's ability to repair DNA is impaired. Mutations accumulate and make the development of tumors more likely and cause microsatellite instability. Microsatellites are normally occurring, repeated sequences of DNA. In cells with mutations in DNA repair genes, some of these microsatellites accumulate errors and change in length. Tests are available that detect microsatellite instability in tumor cells; an MSI-high (MSI-H) histology suggest the presence of a mutated DNA mismatch repair gene and may indicate HNPCC. Testing a tumor sample for microsatellite instability can be useful to determine whether genetic testing for HNPCC is appropriate. (This is one of the two main initial tests performed on colorectal cancer tissue specimens to identify individuals who might have Lynch syndrome.)

**Mismatch Repair (MMR) Mechanism:** The DNA system controlled by certain genes that identifies, excises, and corrects errors in the pairing of the bases during DNA replication. MMR plays a key role in
maintaining genomic stability. Mutations in the genes responsible for this mechanism can lead to certain genetic diseases and some forms of cancer.

**Multigene Panel Tests:** Tests that evaluate more than one (1) gene or gene variant simultaneously to detect changes in gene expression most commonly associated with certain diseases and other genes that may have limited evidence of an association to the disorder. Multigene panel tests may involve traditional exon-by-exon sequencing of targeted genes to identify genetic variants or use next-generation sequencing. Each laboratory establishes its own set of criteria for selecting the genes represented in a panel, even when panels are used for the same or similar clinical indications. The lack of regulatory oversight of genetic testing means that laboratories can change the components of a panel at any time, making it difficult to evaluate the clinical utility of multigene panel tests.

**MutY Homolog (MUTYH)-Associated Polyposis (MAP):** A type of hereditary polyposis syndrome caused by an autosomal recessive trait that carries a high risk for the development of colorectal cancer. Individuals with MAP tend to develop multiple adenomatous colon polyps during their lifetime and are likely to develop polyps and colorectal cancer at a relatively young age, in their 20s to 50s. People with MAP most often resemble the clinical picture of attenuated familial adenomatous polyposis (AFAP), but it has been reported in individuals with clinical symptoms that are consistent with classical familial adenomatous polyposis (FAP) and Lynch syndrome. Individuals with MAP have mutations in both of their mutY homolog (MUTYH) genes (i.e., autosomal recessive trait, one from each biological parent), but patients often have no family history of colon cancer or polyps including their biological parents (although siblings may or may not be affected); therefore genetic testing is used to identify at-risk individuals.

**Next-Generation Sequencing (NGS or Massively Parallel Sequencing):** Genetic testing that involves sequencing of millions of DNA fragments using the following three (3) levels of molecular analysis: (1) Disease-targeted gene panels to sequence genes with an established role in the targeted disease, (2) exome sequencing of coding regions of the genome to include less common variants associated with the disease (i.e., a coding region is the segment of a gene that contains a protein-coding sequence called an exon in all 22,000 genes of the human genome); and (3) genome sequencing of both the coding and non-coding regions of the genome (i.e., the non-coding regions in between exons are called introns). Multiple sequencing platforms and different processes result in variability in test results among laboratories.

**Proband:** The first affected individual in a family who is diagnosed with a genetic disorder, even if affected ancestors are known.

**Second Degree Relative:** A blood relative of an individual who shares approximately 25% of the individual’s genes defined as a biological grandparent, grandchild, aunt, uncle, nephew, niece, or half-sibling.

**Serrated Polyposis Syndrome:** Previously known as hyperplastic polyposis. A clinical diagnosis of serrated polyposis is considered in an individual who meets at least one (1) of the following empiric
Genetic Testing for Hereditary Colorectal Cancer

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14 of 29

criteria: (1) at least 5 serrated polyps (which may include hyperplastic polyps, sessile serrated adenomas/polyps, and/or traditional serrated adenomas) proximal to the sigmoid colon with 2 or more of these being greater than 10 mm; (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; and (3) greater than 20 serrated polyps of any size, but distributed throughout the colon (excluding polyps localized to the rectum and sigmoid unless those polyps are greater than 10 mm or serrations extend beyond widened base). Occasionally, more than one affected case of serrated polyposis is seen in a family. Currently, no causative gene has been identified for serrated polyposis. The risk of colon cancer in this syndrome is elevated, although the precise risk remains to be defined. (Source: National Comprehensive Cancer Network.)

Sessile Serrated Polyp (Sessile Serrated Adenoma): Polyp that displays a lumen with a serrated or stellate architecture. Serrated polyps may or may not be benign. The current classification of serrated lesions of the large intestine includes: hyperplastic polyps, traditional serrated adenomas, and sessile serrated adenomas or polyps with or without cytologic dysplasia.

Third Degree Relative: A blood relative of an individual who shares 12.5% of the individual’s genes as defined as a biological first cousin, great grandmother, or great grandfather.

Whole Exome Sequencing (WES)/ Whole Genome Sequencing (WGS): Sequencing the protein coding regions (called exons) of all of an individual’s genes (known as the exome). While exons represent only 1% of the genome, they account for approximately 85% of disease-causing variants. Through identification of variants across the exome, WES avoids the need to run multiple single-gene tests, which require prior information about variants affecting the disease. WES has been performed in a number of cancers, whereby comparison between tumor DNA and normal DNA from the same individual allows identification of variants specific to the tumor, which may provide information used for diagnosis and treatment. WES is targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses next-generation sequencing techniques to sequence both coding and non-coding regions of the genome.

Applicable Coding

The Plan uses and adopts up-to-date Current Procedural Terminology (CPT) codes from the American Medical Association (AMA), International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes developed by the World Health Organization and adapted in the United States by the National Center for Health Statistics (NCHS) of the Centers for Disease Control under the U.S. Department of Health and Human Services, and the Health Care Common Procedure Coding System (HCPCS) established and maintained by the Centers for Medicare & Medicaid Services (CMS). Because the AMA, NCHS, and CMS may update codes more frequently or at different intervals than Plan policy updates, the list of applicable codes included in this Plan policy is for informational purposes only, may not be all inclusive, and is subject to change without prior notification. Whether a code is listed in the Applicable Coding section of this Plan policy does not

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constitute or imply member coverage or provider reimbursement. Providers are responsible for reporting all services using the most up-to-date industry-standard procedure and diagnosis codes as published by the AMA, NCHS, and CMS at the time of the service.

Providers are responsible for obtaining prior authorization for the services specified in the Medical Policy Statement section and Limitation section of this Plan policy, even if an applicable code appropriately describing the service that is the subject of this Plan policy is not included in the Applicable Coding section of this Plan policy. Coverage for services is subject to benefit eligibility under the member’s benefit plan. Please refer to the member’s benefits document in effect at the time of the service to determine coverage or non-coverage as it applies to an individual member. See Plan reimbursement policies for Plan billing guidelines.

Refer to the Plan’s policy, Genetic Testing Guidelines and Pharmacogenetic, policy number OCA 3.727, for additional guidelines regarding genetic testing. Plan prior authorization is required for all genetic testing, even when the applicable code for the genetic test is not listed in a Plan policy.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description: Codes Covered When Medically Necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (e.g., 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) (e.g., colon cancer, melanoma), gene analysis, V600 variants(s)</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary nonpolyposis 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) (e.g., hereditary nonpolyposis 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 nonpolyposis 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 nonpolyposis 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 nonpolyposis 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 nonpolyposis 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 nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td>81299</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81300</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81301</td>
<td>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</td>
</tr>
<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
</tr>
<tr>
<td></td>
<td>MUTYH (mutY homog [E. coli]) (e.g., MYH-associated polyposis), common variants (e.g., Y165C, G382D)</td>
</tr>
<tr>
<td>Plan note: MUTYH gene sequence testing is considered medically necessary when applicable Plan criteria in the Medical Policy Statement and Limitations sections of this policy are met. This CPT code includes numerous types of tests. See Plan policy, Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727, for prior authorization guidelines for the additional tests included in this CPT code.</td>
<td></td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td></td>
<td>MUTYH (mutY homog [E. coli]) (e.g., MYH-associated polyposis), full gene sequence</td>
</tr>
<tr>
<td>Plan note: MUTYH gene sequence testing is considered medically necessary when applicable Plan criteria in the Medical Policy Statement and Limitations sections of this policy are met. This CPT code includes numerous types of tests. See Plan policy, Genetic Testing Guidelines and Pharmacogenetics (policy number OCA 3.727), for prior authorization guidelines for the additional tests included in this CPT code.</td>
<td></td>
</tr>
<tr>
<td>CPT Code</td>
<td>Description: Code Considered Experimental and Investigational or Medically Necessary Based on Product-Specific Coverage</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>81435</td>
<td>Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis 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</td>
</tr>
<tr>
<td>81436</td>
<td>Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, STK11</td>
</tr>
</tbody>
</table>

CPT Code 81528: Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result.

Plan notes:
1. For Senior Care Options (SCO) members only, Cologuard™ is a covered service using CPT code 81528 (as of 01/01/16) according to the criteria specified in the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3). The type of DNA stool test must be listed as a covered service in NCD 210.3 on the date of the prior authorization request.
2. For all other BMC HealthNet Plan members (except SCO) and Well Sense Health Plan members, this is considered an experimental and investigational service.

Clinical Background Information

Colorectal cancer is the third most common cancer regardless of gender. Worldwide, an estimated 1.4 million cases of colorectal cancer occurred in 2012. About 693,900 deaths from colorectal cancer occurred in 2012 worldwide, accounting for 8% of all cancer deaths. Colorectal cancer may be sporadic, familial, or inherited. Under some circumstances genetic testing is appropriate; it may be offered to high-risk individuals to determine the risk for developing certain genetic forms of colorectal cancer based on clinical indications and/or family history.

Inheritance is a common factor in the pathogenesis of colon cancer with approximately one third of the cases exhibiting an inherited predisposition, while 3% to 5% of cases occur as part of one of the rare but highly penetrant inherited colon cancer syndromes. There are two (2) major types of inherited colorectal cancer: Colorectal cancer caused by hereditary polyposis syndromes and Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC).

Hereditary polyposis syndromes are thought to account for approximately 2% of all colon cancers and include attenuated familial adenomatouos polyposis (AFAP), familial adenomatous polyposis (FAP), and MYH-associated polyposis (MAP). Familial adenomatous polyposis (FAP or classical familial...
adenomatous polyposis) is an autosomal dominant condition characterized by hundreds of polyps in the colon related to mutations of the adenomatous polyposis coli (APC) gene located on chromosome 5q21. Individuals with FAP have certain physical characteristics that can include congenital hypertrophy of retinal pigment epithelium (CHRPE), osteomas, odontomas, supernumerary teeth, epidermoid cysts, desmoids, and duodenal and other small bowel adenomas. The clinical diagnosis of classical FAP is based on the presence of over 100 adenomas or on the documentation of early onset adenomas in an individual with a family history of FAP. Patients with FAP are at risk for thyroid cancer usually occurring after age 30 years. Attenuated FAP or AFAP is a variant of FAP characterized by later onset of disease and fewer than 100 adenomas that typically occur in the right colon.

There is another more rare type of inherited colorectal cancer called MYH-associated polyposis or MAP. This type is a hereditary autosomal recessive colorectal cancer syndrome characterized by multiple adenomatous colon polyps. It is associated with mutations in the MUTYH gene, specifically Y165C and/or G382D. Individuals with MAP are at risk for developing colon cancer at young ages (30s and 40s). There may also be an increased risk of polyps in the small intestine. Often individuals with MAP will not have a family history of colon polyps or colon cancer because of the autosomal recessive pattern that indicates the genetic defect must be inherited from both parents.

According to the National Comprehensive Cancer Network (NCCN), hereditary nonpolyposis colorectal cancer (HNPPCC) or Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases. Clinical features of HNPPCC include early (before age 50) onset and a smaller number of adenomatous polyps that usually occur in the right proximal end of the colon. HNPPCC is associated with an increased risk of endometrial cancer in women (including individuals born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes) as well as other cancers that include ovarian, stomach, ureter/renal pelvis, liver and biliary tract, small bowel, and brain. Criteria have been developed to identify patients who should be tested for possible Lynch syndrome, including Amsterdam II criteria and revised Bethesda guidelines. Approximately 50% of families meeting the Amsterdam II criteria (established in 1999) have a mutation in an MMR gene. The National Cancer Institute introduced the revised Bethesda guidelines in 2002 to clarify selection criteria and have shown to be beneficial identifying the patients who should undergo further testing.

For patients with colorectal cancer being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test or the immunohistochemistry (IHC) test with or without BRAF gene mutation testing should be used as an initial evaluation of tumor tissue prior to mismatch repair mechanism (MMR); i.e., testing of tumor tissue for inherited mutation in a DNA mismatch repair gene analysis. Consideration of proceeding to MMR gene sequencing would depend on results of MSI or the IHC testing.

In summary, genetic testing for HNPPCC, FAP/AFAP, or MAP is used to determine if an individual has an increased susceptibility for colorectal cancer. A detailed family history, medical and surgical history and physical examination are essential in screening for inherited colorectal cancer syndromes. In addition, the American Society of Clinical Oncology recommends informed consent for cancer genetic testing for hereditary colorectal cancer.

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testing that includes implications for positive and negative results, information on the specific test being performed, possibility that the test may not be informative, options for risk assessment without genetic testing, risk of passing the mutation to children, technical accuracy of the test, risk of psychological distress and options for medical surveillance and screening following testing.

References


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Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for COLORECTAL CANCER Screening Tests (210.3). Effective Date: October 9, 2014. Implementation Date: "Plan refers to Boston Medical Center Health Plan, Inc. and its affiliates and subsidiaries offering health coverage plans to enrolled members. The Plan operates in Massachusetts under the trade name Boston Medical Center HealthNet Plan and in other states under the trade name Well Sense Health Plan."
Genetic Testing for Hereditary Colorectal Cancer

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September 8, 2015. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=281&ncdver=5&CovSelection=Both&ArticleType=All&PType=Final&s=Massachusetts&KeyWord=colorectal+cancer&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAABAAAAAA%3d%3d&


Gene Testing for Hereditary Colorectal Cancer

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Genetic Testing for Hereditary Colorectal Cancer

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<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date* and Version Number</th>
<th>Policy Owner</th>
<th>Approved by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Approval: N/A</td>
<td>07/03/07 Version 1</td>
<td>Medical Policy Manager as Chair of Medical Policy, Criteria, and Technology Assessment Committee (MPCTAC) and member of Quality Improvement Committee (QIC)</td>
<td>Utilization Management Committee (UMC) and QIC</td>
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<tr>
<td>Internal Approval: 04/24/07: UMC 05/03/07: QIC</td>
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</table>

*Effective Date for the BMC HealthNet Plan Commercial Product(s): 01/01/12
*Effective Date for the Well Sense Health Plan New Hampshire Medicaid Product(s): 01/01/13
*Effective Date for the Senior Care Options Product(s): 01/01/16

<table>
<thead>
<tr>
<th>Review Date</th>
<th>Summary of Revisions</th>
<th>Revision Effective Date and Version Number</th>
<th>Approved by</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/08/08</td>
<td>Review summary of changes: Added criteria for the coverage of genetic testing for MYH associated polyposis (MAP) mutations. Added that fecal DNA testing is considered investigational.</td>
<td>Version 2</td>
<td>04/08/08: MPCTAC 04/22/08: UMC 04/25/08: QIC</td>
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<tr>
<td>04/28/09</td>
<td>Updated references, no criteria changes.</td>
<td>Version 3</td>
<td>04/28/09: MPCTAC 04/28/09: UMC</td>
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</table>

Genetic Testing for Hereditary Colorectal Cancer

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<th>Version</th>
<th>Date</th>
<th>MPCTAC</th>
<th>QIC</th>
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<tbody>
<tr>
<td>04/01/10</td>
<td>Updated references, no criteria changes.</td>
<td>Version 4</td>
<td>04/27/10: MPCTAC 05/26/10: QIC</td>
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<tr>
<td>04/01/11</td>
<td>Revised clinical criteria for HNPCC genetic mutation testing for the MLH1 or MSH2 mutations to be medically necessary when either the Amsterdam II criteria or the revised Bethesda Guidelines are met OR when endometrial cancer is diagnosed before age 50 and updated references.</td>
<td>Version 5</td>
<td>04/20/11: MPCTAC 05/25/11: QIC</td>
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<tr>
<td>12/01/11</td>
<td>Added new 2012 CPT codes.</td>
<td>Version 6</td>
<td>12/01/11: MPCTAC 12/01/11: QIC</td>
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<tr>
<td>04/01/12</td>
<td>Updated references and deleted diagnosis codes.</td>
<td>Version 7</td>
<td>04/18/12: MPCTAC 04/18/12: QIC</td>
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<tr>
<td>06/01/12</td>
<td>Added clarification regarding the use of Tier 1 and 2 molecular pathology codes, updated CPT codes to include methodology codes, and revised the introductory paragraph in Applicable Coding section.</td>
<td>Version 8</td>
<td>06/20/12: MPCTAC 06/27/12: QIC</td>
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<tr>
<td>07/29/12:</td>
<td>Off cycle review for Well Sense Health Plan, revised Description of Item or Service section.</td>
<td>Version 9</td>
<td>08/03/12: MPCTAC 09/05/12: QIC</td>
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<tr>
<td>09/01/12</td>
<td>Review for effective date 01/01/13. Updated and added references. Removed deleted codes from applicable code list. Revised the following sections: Summary, Description of Item or Service, Clinical Guideline Statement, Definitions, and Clinical Background Information. Added EPCAM genetic testing and clinical criteria for test. Revised clinical criteria for FAP/AFAP, HNPCC, and MAP genetic mutation testing. Added reference to Experimental and Investigational Treatment policy.</td>
<td>01/01/13 Version 10</td>
<td>09/19/12: MPCTAC 10/24/12: QIC</td>
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<tr>
<td>08/14/13 and 08/15/13</td>
<td>Off cycle review for Well Sense Health Plan and merged policy format. Incorporate policy revisions dated 09/01/12 (as specified above) for the Well Sense Health Plan product; these policy revisions were approved by MPCTAC on 09/19/12 and QIC on 10/24/12 for applicable Plan products.</td>
<td>Version 11</td>
<td>08/14/13: MPCTAC (electronic vote) 08/15/13: QIC</td>
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<tr>
<td>10/01/13</td>
<td>Review for effective date 02/01/14. Updated applicable code list. Revised criteria in Medical Policy Statement section. Revised Summary, Description of Item or Service, Definitions, Limitations, and Clinical Background Information.</td>
<td>02/01/14 Version 12</td>
<td>10/16/13: MPCTAC 11/21/13: QIC</td>
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</table>
### Policy Revisions History

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
<th>Effective Date</th>
<th>Version</th>
<th>Review Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/14</td>
<td>Review for effective date 10/01/14. Added CPT code 81404 to the applicable code list. Updated Summary section.</td>
<td>10/01/14</td>
<td>Version 13</td>
<td>07/21/14: MPCTAC (electronic vote)</td>
</tr>
<tr>
<td>10/01/14, 11/01/14, and 12/01/14</td>
<td>Review for effective date 03/01/15. Updated Summary, Description of Item or Service, Definitions, and Clinical Background Information sections. Updated criteria in the Medical Policy Statement section. Removed the following 2014 deleted codes: HCPCS code S3833 and HCPCS code S3834. Added CPT codes 81435, 81436, and 81288 as applicable codes. Changed annual review schedule.</td>
<td>03/01/15</td>
<td>Version 14</td>
<td>10/15/14: MPCTAC</td>
</tr>
<tr>
<td>11/25/15</td>
<td>Review for effective date 01/01/16. Updated template with list of applicable products and notes. Updated Summary section. Revised language in the Applicable Coding section.</td>
<td>01/01/16</td>
<td>Version 15</td>
<td>11/18/15: MPCTAC (electronic vote)</td>
</tr>
<tr>
<td>04/20/16</td>
<td>Revision effective 04/20/16. Removed HCPCS code G0464 from the Applicable Coding section because this is an industry-wide deleted code as of 01/01/16. This code was formerly listed as an experimental and investigational service.</td>
<td>04/20/16</td>
<td>Version 16</td>
<td>Not applicable because industry-wide deleted code.</td>
</tr>
<tr>
<td>01/01/16</td>
<td>Review for effective date 05/01/16. Updated criteria in the Medical Policy Statement and Limitations sections. Updated Summary, Definitions, Clinical Background Information, and References sections. Revised codes and revised notes in the Applicable Coding section.</td>
<td>05/01/16</td>
<td>Version 17</td>
<td>01/20/16: MPCTAC</td>
</tr>
<tr>
<td>09/28/16</td>
<td>Review for effective date 11/01/16. Administrative changes made to clarify language related to gender.</td>
<td>11/01/16</td>
<td>Version 18</td>
<td>09/30/16: MPCTAC (electronic vote)</td>
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**Last Review Date**

09/28/16

**Next Review Date**

12/01/16

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Authorizing Entity

QIC

Other Applicable Policies

Medical Policy - Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies, policy number OCA 3.573
Medical Policy - Experimental and Investigational Treatment, policy number OCA 3.12
Medical Policy - Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests), policy number OCA 3.572
Medical Policy - Genetic Testing for Familial Malignant Melanoma, policy number OCA 3.78
Medical Policy - Genetic Testing for Fragile X-Associated Disorders, policy number OCA 3.571
Medical Policy - Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727
Medical Policy - Genetic Testing for Hereditary Breast and Ovarian Cancer, policy number OCA 3.57
Medical Policy - Genetic Testing for Hereditary Thrombophilia, policy number OCA 3.728
Medical Policy - Medically Necessary, policy number OCA 3.14
Medical Policy - Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening), policy number OCA 3.726

Reference to Applicable Laws and Regulations

Massachusetts General Law. Chapter 111. Section 70G. (M.G.L. c. 111 sec. 70G.) Genetic information and reports protected as private information; prior written consent for genetic testing. Accessed at: https://malegislature.gov/Laws/GeneralLaws/PartI/TitleXVI/Chapter111/Section70G

Disclaimer Information: *

Medical Policies are the Plan’s guidelines for determining the medical necessity of certain services or supplies for purposes of determining coverage. These Policies may also describe when a service or supply is considered experimental or investigational, or cosmetic. In making coverage decisions, the Plan uses these guidelines and other Plan Policies, as well as the Member’s benefit document, and when appropriate, coordinates with the Member’s health care Providers to consider the individual Member’s health care needs.

Plan Policies are developed in accordance with applicable state and federal laws and regulations, and accrediting organization standards (including NCQA). Medical Policies are also developed, as appropriate, with consideration of the medical necessity definitions in various Plan products, review of current literature, consultation with practicing Providers in the Plan’s service area who are medical experts in the particular field, and adherence to FDA and other government agency policies. Applicable state or federal mandates, as well as the Member’s benefit document, take precedence over these guidelines. Policies are reviewed and updated on an annual basis, or more frequently as needed. Treating providers are solely responsible for the medical advice and treatment of Members.

The use of this Policy is neither a guarantee of payment nor a final prediction of how a specific claim(s) will be adjudicated. Reimbursement is based on many factors, including member eligibility and benefits on the date of service; medical necessity; utilization management guidelines (when applicable); coordination of benefits; adherence with applicable Plan policies and procedures; clinical coding criteria; claim editing logic; and the applicable Plan – Provider agreement.

Genetic Testing for Hereditary Colorectal Cancer

* Plan refers to Boston Medical Center Health Plan, Inc. and its affiliates and subsidiaries offering health coverage plans to enrolled members. The Plan operates in Massachusetts under the trade name Boston Medical Center HealthNet Plan and in other states under the trade name Well Sense Health Plan.