Medical Policy

Genetic Testing for Hereditary Colorectal Cancer

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Product Applicability  

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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. See the Plan’s Genetic Testing and Pharmacogenetics medical policy (policy number OCA 3.727) rather than this Plan policy for medically necessary indications for genetic testing to predict the effectiveness of cancer treatment. **Plan prior authorization is required for all molecular and chromosomal genetic testing**, except for prenatal genetic screening tests for a member with one of the pregnancy diagnosis codes specified in the Applicable Coding section of the Genetic Testing Guidelines and Pharmacogenetics medical policy (policy number OCA 3.7272), Chromosomal...
Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies medical policy (policy number OCA 3.573), or Genetic Testing for Fragile X-Associated Disorders medical policy (policy number OCA 3.571) when applicable Plan criteria are met. Biochemical genetic tests used to study the amount or activity level of proteins to indicate changes to the DNA require prior authorization only when the test is included in the Applicable Coding section of a Plan genetic testing medical policy.

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 genetics. 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 for BMC HealthNet Plan members (or at www.SeniorsGetMore.org for Senior Care Options members) and 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
4. Genetic Testing for Fragile X-Associated Disorders, policy number OCA 3.571
5. Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727
6. Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome, policy number OCA 3.57
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

Genetic Testing for Hereditary Colorectal Cancer

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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 (previously known as hereditary nonpolyposis colorectal cancer or 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 tumor 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 (and defined in the Definitions section of this policy): 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 Lynch syndrome (previously termed hereditary nonpolyposis colorectal cancer or HNPCC).

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. Applicable Plan criteria must be met for blood-based genetic testing for the following conditions, as specified below in item A (for FAP or AFAP) or item B (for MAP). As stated in the Limitations section of this policy, Plan Medical Director review and approval are required for the use of multigene panels when used as an alternative to targeted genetic testing.

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

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

   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. Member has a personal history of multifocal, bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE), a pigmented fundus lesion of the retina associated with FAP; OR

   f. For predictive testing in a high-risk member age 10 or older who is a first-degree relative (i.e., full biological sibling, biological parent, or biological child) of an affected individual and/or proband with a disease causing mutation for FAP or AFAP and/or a known APC mutation; OR

   g. 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 a member with a personal history of adenomatous polyposis (10 or more adenomas); OR

   Note: According to NCCN guidelines, MUTYH genetic testing is NOT indicated for a personal history of a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or CHRPE. 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. For predictive testing in a high-risk member age 18 or older who is a first-degree relative (i.e., full biological sibling, biological parent, or biological child) of an affected individual and/or proband with a known deleterious MUTYH mutation and findings are consistent with recessive inheritance; OR

c. The member has a personal history of serrated polyposis syndrome and meets at least ONE (1) of the following criteria, as specified below in items (1) through (3):

(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 with two (2) or more of these being larger than 10 mm in size; OR

(2) Personal history of any number of serrated polyps (which may include hyperplastic polyps, sessile serrated adenomas/polyps, and/or traditional serrated adenomas) proximal to the sigmoid colon in a member who has a first-degree relative (i.e., full biological sibling, biological parent, or biological child) with serrated polyposis; OR

(3) 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 Lynch Syndrome (Previously Termed Hereditary Nonpolyposis Colorectal Cancer or HNPCC):

There are different approaches to evaluation of Lynch syndrome: Genetic testing of sequence variants (including reflex testing for large genomic rearrangements) in high-risk and affected members, microsatellite instability (MSI) of tumor tissue, and immunohistochemistry (IHC) of tumor tissue. As stated in the Limitations section of this policy, Plan Medical Director review and approval are required for the use of multigene panels to diagnosis of Lynch syndrome when used as an alternative to targeted, syndrome-specific genetic testing or when tumor tissue is not available or insufficient for genetic testing. The following applicable criteria must be met for genetic testing for Lynch syndrome, as specified below in item A for blood-based genetic testing to evaluate mismatch repair mechanism (MMR) genes, item B for genetic testing of tumor tissue with immunohistochemistry (IHC) and microsatellite instability (MSI), and/or item C for genetic testing for EPCAM gene variant testing (using blood-based genetic testing or testing of tumor tissue).
A. **Criteria for Blood-Based Genetic Testing to Evaluate MMR Genes (i.e., MLH1, MSH2, MSH6, and PMS2) to Diagnose Lynch Syndrome:**

Deleterious mutations in any of the four (4) mismatch repair mechanism (MMR) genes (i.e., MLH1, MSH2, MSH6, and PMS2) or EPCAM (not a mismatch repair gene) are diagnostic for Lynch syndrome. See criteria in item C (Criteria for Genetic Testing of EPCAM Gene to Diagnose Lynch Syndrome Using Tumor Tissue or Blood-Based Testing) rather than this section for guidelines related to EPCAM testing.

Blood-based genetic testing of the MMR genes MLH1, MSH2, MSH6, and PMS2 is considered medically necessary for at least ONE (1) of the following indications when applicable Plan criteria are met: (1) Predictive genetic testing for a high-risk member; (2) genetic testing of affected member when no tumor tissue is available or there is an insufficient tumor sample; or (3) when the treating provider has determined that blood-based MMR germline mutation testing is medically necessary in addition to genetic testing of tumor tissue to make a definitive diagnosis of Lynch syndrome. BOTH of the following criteria must be met for blood-based genetic testing of the MMR genes (i.e., MLH1, MSH2, MSH6, and PMS2) to diagnose Lynch syndrome, 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. The member is diagnosed with endometrial cancer before 50 years of age (for the diagnosis of Lynch syndrome); OR

   b. The member is diagnosed with colorectal cancer before 50 years of age (for the diagnosis of Lynch syndrome); OR

   c. EITHER the Amsterdam II criteria or the Revised Bethesda guidelines are met for a member age 18 or older on the date of testing (including an unaffected member when applicable family history criteria are met or a member with endometrial cancer or colorectal cancer according to the applicable age criterion for testing), as specified below in item (1) for Amsterdam II criteria or item (2) revised Bethesda guidelines:

   (1) **Amsterdam II Criteria:**

   Member has with three (3) or more biological relatives who have had cancer associated with Lynch syndrome** or documented Lynch syndrome and ALL of the following criteria related to family medical history must be present, as specified below in items (a) through (e):

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(a) One (1) relative must be a first-degree relative of the other two (2); AND

(b) At least two (2) successive generations of the member’s biological family must be affected; AND

(c) At least one (1) of these biological relatives with cancer associated with Lynch syndrome** or known Lynch syndrome has been diagnosed before 50 years of age; AND

(d) FAP has been excluded in these familial colorectal cancer cases (if any); AND

(e) Tumors of these familial cancers associated with Lynch syndrome** or known Lynch syndrome have been verified by pathological examination, whenever possible; OR

(2) **Revised Bethesda Guidelines:**

Member must meet at least ONE (1) of the following criteria related to personal medical history, as specified below in items (a) through (e):

(a) Member diagnosed with colorectal cancer before 50 years of age; OR

(b) Member with synchronous or metachronous colorectal tumors or other Lynch syndrome-related tumors** regardless of age; OR

(c) Member diagnosed before 60 years of age with colorectal cancer with the microsatellite instability-high (MSI-H) tumor histology; OR

(d) Member diagnosed with colorectal cancer at any age with one (1) or more first-degree relatives with a Lynch syndrome-related cancer** or known Lynch syndrome with one (1) of these cancers diagnosed before 50 years of age; OR

(e) Member diagnosed with colorectal cancer at any age and with two (2) or more first- or second-degree relatives with Lynch syndrome-related cancer** or known Lynch syndrome at any age; OR

** 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.
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 a member satisfying the Amsterdam II criteria or Revised Bethesda guidelines (as specified above); OR

(2) A first-degree or second-degree relative of a member with a known MMR mutation or EPCAM 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/EPCAM mutations determined by clinical presentation, as determined by the treating specialist); AND/OR

B. Criteria for Tumor Tissue Genetic Testing Using Immunohistochemistry (IHC), Microsatellite Instability (MSI) and/or Molecular Testing to Diagnose Lynch Syndrome:

Examples of genetic testing of tumor tissue using IHC or MSI to diagnose Lynch syndrome include the following: BRAF mutation analysis (for colorectal cancer tumor tissue only), Lynch syndrome MSI, and/or IHC expression of MMR proteins (MLH1, MSH2, MSH6, and PMS2 genes) in endometrial or colon cancer tumor tissue. See criteria below in item C (Criteria for Genetic Testing of EPCAM Gene to Diagnose Lynch Syndrome Using Tumor Tissue or Blood-Based Testing) rather than this section for guidelines related to EPCAM testing. Genetic testing of tumor tissue (colorectal cancer tumor tissue or endometrial cancer tissue when clinically appropriate, as stated below) using IHC and MSI (using either testing methodology or both performed in conjunction) is considered medically necessary when at least ONE (1) of the following criteria is met, as specified below in items 1 through 6:

1. Member diagnosed with endometrial cancer before 50 years of age; OR

2. Member diagnosed with colorectal cancer at 70 years of age or younger; OR

3. Member with -synchronous or metachronous colorectal tumors or other Lynch syndrome-related tumors** regardless of age; OR

4. Member with colorectal cancer with microsatellite instability-high (MSI-H) diagnosed 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

5. Member diagnosed with colorectal cancer at any age with one (1) or more first-degree relatives with an Lynch syndrome-related cancer** or known Lynch syndrome, with one (1) of these cancers diagnosed under age 50 years; OR

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6. Member diagnosed with colorectal cancer at any age with two (2) or more first- or second-degree relatives with Lynch syndrome-related cancer** or known Lynch syndrome at any age; AND/OR

** 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. **Criteria for Genetic Testing of EPCAM Gene Variants to Diagnose Lynch Syndrome Using Tumor Tissue or Blood-Based Testing:**

Germline deletions in the EPCAM gene may inactivate the MSH2 gene in individuals with Lynch syndrome; EPCAM testing is a valuable diagnostic tool for Lynch syndrome when no pathogenic or potentially pathogenic variant is identified in MSH2. EPCAM variant testing may be conducted concurrently or sequentially to MMR gene variant analysis, as determined by the treating provider (according to guidelines established by the National Comprehensive Cancer Network). Blood-based genetic testing of the EPCAM gene is considered medically necessary for at least ONE (1) of the following indications when applicable Plan criteria are met: (1) Predictive genetic testing for a high-risk member; (2) genetic testing of a member with colorectal cancer when no tumor tissue is available or there is an insufficient tumor sample; or (3) when the treating provider has determined that blood-based EPCAM testing is medically necessary in addition to genetic testing of tumor tissue to make a definitive diagnosis of Lynch syndrome. EPCAM genetic variant testing of colorectal cancer tumor tissue may be used to diagnose Lynch syndrome in an affected member.

EPCAM gene mutation testing (using EPCAM molecular testing in tumor tissue or blood-based EPCAM variant testing) is considered medically necessary when BOTH of the following criteria are 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 c:

   a. EPCAM genetic testing for a member with colorectal cancer, for the diagnosis of Lynch syndrome, when at least ONE (1) of the following criteria are met, as specified below in items (1) through (3):

   (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 on the date of testing 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. The use of SEPT9 methylation testing for colorectal cancer is considered experimental and investigational due to insufficient studies that document the clinical utility of this type of test to detect colorectal cancer. Using DNA extraction from patient plasma, the SEPT9 methylation assay is based on the finding that there is a significant difference in SEPT9 methylation between individuals with colorectal cancer and those with normal colorectal tissue. Examples of this type of testing include but are not limited to the following: ColoVantage™ - Methylated Septin 9 (by Quest Diagnostics Inc.), Epi proColon (Epigenomics Inc.), Septin 9 (SEPT9) - Methylated DNA Detection by Real-Time PCR (by ARUP Laboratories)

3. 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.
4. A request for genetic testing of a member before the applicable minimum age criterion (i.e., minimum age of 10 for APG gene predictive testing, minimum age of 18 for MAP predictive testing, and minimum age of 18 for Lynch syndrome predictive testing) for an at-risk member who otherwise meets applicable medical necessity criteria will require Plan Medical Director review for individual consideration based on the member’s personal medical history, family medical history and supports, treatment plan based on test results, and clinical indications for testing.

5. Plan Medical Director review and approval are 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 (Ambry Genetics Corp.), ColoNext (Ambry Genetics Corp.), High/Moderate Risk Panel (GeneDx Inc.), iGene Cancer Panel (ApolloGen Molecular Diagnostics Laboratory), Preventest (GeneID Advanced Molecular Diagnostics LLC), and VistaSeq Hereditary Cancer Panel (Laboratory Corporation of America).

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 to predict the susceptibility to hereditary colorectal cancer due to limited 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. For multigene panel testing to be considered medically necessary, medical record documentation must be submitted to the Plan with the prior authorization request demonstrating that ALL of the following criteria are met (and after approval by a Plan Medical Director), with criteria specified below in items a through g:

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 medical history, biological family medical history, or treatment plan for the member being tested and there are professional society management guidelines or National Comprehensive National

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Comprehensive Cancer Network (NCCN) guidelines (with applicable references provided with the prior authorization request) documenting the clinical utility of testing for the members who test positive for any and all genes in the panel;¹ OR

¹ Note: According to NCCN Guidelines Version 2.2016 for Genetics/Familial High-Risk Assessment: Colorectal, “The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a mutation known to be clinically actionable...”

d. The results of the requested multigene panel will directly impact the treatment plan and clinical decision-making process for the member being tested; AND

e. There are no other known causative circumstances or factors (e.g., environmental exposures, injury, infection) that can explain the member’s symptoms or medical condition; AND

f. Multigene panel testing is more practical testing to diagnose the member’s condition than the separate single gene tests or targeted panels that would be recommended (with supporting documentation provided); AND

g. The member’s clinical presentation does not fit a well-described syndrome for which single-gene testing, targeted panel testing, or chromosomal microarray analysis is currently available for the member’s condition or is not clinically appropriate for the member (with supporting clinical documentation provided).

The Plan considers the multigene panel testing to be medically necessary only when ALL of the criteria outlined above (in items a through g) are met; disease-targeted genetic testing is considered medically necessary as an alternative when Plan criteria are met in the Medical Policy Statement section (and according to guidelines specified in the Limitations section of this policy). See the 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 and the use of multigene panels to determine hereditary cancer susceptibility for other types of cancer.

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 investigational treatment. Review Plan policy, Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727, for Plan genetic testing guidelines not outlined in this policy, including but not limited to predicting effectiveness of treatment, 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.

**BRAF Gene Mutation Testing of Colorectal Cancer Tissue**: Testing of colorectal tumor tissue is used to identify genetic variants in the BRAF sequence p.Val600Glu (commonly referred to as V600E) to diagnosis Lynch syndrome. Sequence variants in BRAF are associated with MLH1 gene silencing with individuals with sporadic colorectal cancer. Abnormal MLH1 immunohistochemistry (IHC) should be followed by colorectal tumor tissue for the presence of BRAF V600E mutation (or with IHC with BRAF)
or hypermethylation of the MLH1 promoter, which are associated with sporadic colorectal tumors. BRAF V600E mutation tumor testing is not informative for endometrial tumors and therefore does not apply to endometrial cancer.

**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 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-Tract (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

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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.

2. Chromosomal genetic tests analyze whole chromosomes to see if there are large genetic changes, such as an extra copy of a chromosome or missing DNA, 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:** Previously termed hereditary nonpolyposis colorectal cancer (or HNPCC), Lynch syndrome is the most common form of hereditary colorectal cancer. The syndrome is 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, and/or PMS2). Defects in DNA mismatch repair result in microsatellite instability (MSI). MLH1 and MSH2 germline pathogenic variants account for approximately 90% of pathogenic variants in families with Lynch syndrome; MSH6 pathogenic variants in about 7%-10%; and PMS2 pathogenic variants in fewer than 5%. Germline deletions in EPCAM (not a mismatch repair gene) inactivate MSH2 in about 1% of individuals with Lynch syndrome and therefore such deletions are associated with Lynch syndrome. 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 stops working, an individual can develop Lynch syndrome.
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 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

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intron). 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 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)**: WES captures and sequences at a deep level the protein coding regions (called exons) of an individual’s genes using first-generation sequencing techniques or next-generation sequencing to detect disease-causing variants and discover gene targets. 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. Because WES only evaluates the protein-coding regions of the
human genome (exoms), WES is a more cost-effective alternative to WGS. WES produces a smaller, more manageable data set with faster turnaround time for analyses than WGS. WGS has the ability to detect structural variations located outside of the exome that may be related to many diseases and cannot be identified with WES. WES and WGS have been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases, but there remain issues of error rates due to technical challenges and difficulty interpreting potential causative variants from variants of unknown significance generated for each patient. Examples of tests include but are not limited to the following: TruGenome tests (Illumina), Endometrial Cancer Panel (GeneDx), ExomeNext and ExomeNext-Rapid (Ambyr Genetics), XomeDx™ test (GeneDx), mtSEEK Whole Mitochondrial Genome Analysis (Courtagen Life Sciences Inc.), and/or nucSEEK Comprehensive Sequence Analysis of Nuclear Mitochondrial Exome (Courtagen Life Sciences, Inc.). According to The American College of Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole genome or whole exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. See the Genetic Testing Guidelines and Pharmacogenetics medical policy (policy number OCA 3.727) rather than this policy for Plan guidelines related to WES and WGS.

**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 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 colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
</tr>
<tr>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81293</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81294</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81296</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81297</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis 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>
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<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>Code</td>
<td>Description</td>
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</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>
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<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>81327</td>
<td>SEPT9 (Septin9) (e.g., colorectal cancer) methylation analysis</td>
</tr>
<tr>
<td></td>
<td>Plan note: See the Limitations section of this Plan policy for SEPT9 methylation testing of members for colorectal cancer screening.</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></td>
<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>
</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></td>
<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>
</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>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description: Code Considered Experimental and Investigational or Medically Necessary Based on Product-Specific Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>81528</td>
<td>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 &amp; 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.</td>
</tr>
</tbody>
</table>

**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 adenomatous 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, Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC) is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases. Clinical features of HNPCC include early (before age 50) onset and a smaller number of adenomatous polyps that usually occur in the right proximal end of the colon. HNPCC 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. According to the American Medical Association (AMA) and the National Coalition for Health Professional Education in Genetics (NCHPEG), priority should be given to performing genetic testing of tumor tissue from colorectal cancer or endometrial adenocarcinoma of an affected family member when screening Lynch syndrome in high-risk families. If both the blood and tumor specimens have a documented gene mutation suggestive of Lynch syndrome, the condition is inherited rather than acquired.

In summary, genetic testing for Lynch syndrome, 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 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.

At the time of the Plan’s most recent policy review, the Centers for Medicare & Medicaid Services (CMS) has implemented the following national coverage determinations (NCDs) related to genetic tests: NCD for Colorectal Cancer Screening Tests (210.3) for coverage of immunoassay and guaiac fecal occult blood tests and the Cologuard™ - Multitarget Stool DNA (sDNA) test when CMS applicable criteria are met, NCD for Pharmacogenomic Testing for Warfarin Response (90.1) for medically necessary indications for testing as determined by CMS, and NCD for Cytogenetic Studies (190.3) for coverage based on CMS guidelines. Medicare uses a combination of national and local coverage determinations for making coverage decisions for genetic tests. Medicare administrative contractors (MAC) may implement local coverage determinations (LCDs) that apply only within their own jurisdictions. Verify if applicable CMS criteria are in effect (through an NCD, LCD, or other CMS guidelines) for the specified genetic test, product name, site-specific gene analysis, and the indication for testing on the date of the prior authorization request for a Senior Care Options member.

References


Genetic Testing for Hereditary Colorectal Cancer

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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 September 8, 2015. Accessed 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=gAAAAABAAA%3d%3d&

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Cytogenetic Studies (190.3). July 16, 1998. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=198&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=cytogenetic&KeyWordLookUp=Title&KeyWordSearchType=And&lcd_id=24308&lcd_version=26&basket=lcd*3a%2424308*3a%2426*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257C+LLC+(03102)*3a%24&bc=gAAAAACAAA%3d%3d&


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Genetic Testing for Hereditary Colorectal Cancer

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Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, and Levin TR. Genetic Testing for Hereditary Colorectal Cancer

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Genetic Testing for Hereditary Colorectal Cancer

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Genetic Testing for Hereditary Colorectal Cancer


<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>
</tr>
<tr>
<td>Internal Approval: 04/24/07: UMC 05/03/07: QIC</td>
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</tbody>
</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

Policy Revisions History

<table>
<thead>
<tr>
<th>Review Date</th>
<th>Summary of Revisions</th>
<th>Revision Effective Date and Version Number</th>
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</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Date</th>
<th>Description</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>
</tr>
<tr>
<td>04/28/09</td>
<td>Updated references, no criteria changes.</td>
</tr>
<tr>
<td>04/01/10</td>
<td>Updated references, no criteria changes.</td>
</tr>
<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>
</tr>
<tr>
<td>12/01/11</td>
<td>Added new 2012 CPT codes.</td>
</tr>
<tr>
<td>04/01/12</td>
<td>Updated references and deleted diagnosis codes.</td>
</tr>
<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>
</tr>
<tr>
<td>07/29/12</td>
<td>Off cycle review for Well Sense Health Plan, revised Description of Item or Service section.</td>
</tr>
<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>
</tr>
<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</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Date</th>
<th>Action Description</th>
<th>Effective Date</th>
<th>Version</th>
<th>Reviewing Body</th>
</tr>
</thead>
<tbody>
<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 sections. Updated references.</td>
<td>02/01/14</td>
<td>Version 12</td>
<td>10/16/13: MPCTAC</td>
</tr>
<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. 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</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>12/09/15: QIC</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>
</tr>
<tr>
<td>12/01/16</td>
<td>Review for effective date 04/01/17. Industry-wide new applicable code added and Plan note added to Applicable Coding section. Revised criteria in the Medical Policy Statement and Limitations section. Updated Policy Summary,</td>
<td>04/01/17</td>
<td>Version 19</td>
<td>12/21/16: MPCTAC</td>
</tr>
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Policy Revisions History

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<tr>
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<th>Authorizing Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/01/17</td>
<td>Review for effective date 05/01/17. Revised criteria for multigene panel testing in the Limitations section. Updated definition of WES and WGS.</td>
<td>05/01/17 Version 20</td>
<td>01/18/17: MPCTAC 02/08/17: QIC</td>
</tr>
</tbody>
</table>

Last Review Date

01/01/17

Next Review Date

12/01/17

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 Syndrome, 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

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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.