CLINICAL MEDICAL POLICY	
Policy Name:	Genetic Testing for Colorectal Cancer Susceptibility
Policy Number:	MP-018-MD-DE
Responsible Department(s):	Medical Management
Provider Notice Date:	10/15/2018; 10/01/2017
Issue Date:	11/15/2018
Original Effective Date:	11/15/2018; 11/01/2017
Annual Approval Date:	09/11/2019
Revision Date:	09/11/2018; 08/09/2017; 03/14/2017
Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 14

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Option provides coverage under the laboratory medical-surgical benefits of the Company's Medicaid products for medically necessary genetic testing for colorectal cancer susceptibility.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

BRAF - (serine/threonine-protein kinase B-Raf, v-Raf murine sarcoma viral oncogene homolog B1) – The BRAF gene is located on chromosome arm 7q34. It encodes B-Raf, a serine/threonine kinase that is part of the Ras-Raf-Mek-Erk-MAPK signaling cascade. Changes or mutations to the BRAF gene can cause uncontrolled cell growth, which may lead cancer.

Genetic testing – Genetic testing requires the analysis of human chromosomes, DNA (deoxyribonucleic acid), RNA (ribonucleic acid), genes or gene products in order to detect or predict risk of inherited or non-inherited genetic variants related to disease, identify carriers, establish prenatal and clinical diagnosis or prognosis.

Genetic Counseling – The process in which a specially trained professional evaluates family history, medical records, and genetic test results, in the risk assessment of an individual for genetic disease, understanding the limitations and risks of genetic testing.

Epithelial Cellular Adhesion Molecule Gene (EPCAM) – This gene provides instructs for making a protein known as epithelial cellular adhesion molecule. This protein is found in epithelial cells which are cells that line the surfaces and cavities of the body. Mutations in this gene have been related to Lynch syndrome.

Familial adenomatous polyposis (FAP) – An inherited disorder characterized by the presence of adenomatous polyps throughout the colon than can commonly progress into colon cancer.

Hereditary nonpolyposis colorectal cancer (HNPCC [Lynch syndrome]) – An inherited colorectal cancer syndrome that accounts for 5% to 8% of all colorectal cancers.

Direct Risk – When there is documentation in the family history of a disorder that involves an autosomal dominant inheritance which has been demonstrated in either the mother or the father or evidence of a disorder inherited in an autosomal recessive or X-linked recessive manner with supporting documentation suggestive of family history of a suspected disorder.

Family –

- First degree relatives are defined blood relatives with whom an individual shares approximately 50% of his/her genes such as the parents, brothers, sisters, or children of an individual member;
- Second degree relatives are those people with whom one quarter of the member's genes is shared (e.g., grandparent, grand child, uncle, aunt, nephew, niece or half-sibling).
- Third degree relatives are those people with whom one eighth of a member's genes is shared (e.g., cousin, great grandparent, great aunt, or great uncle)

Next-generation sequencing – A technique that allows rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. This technology includes but is not limited to massively parallel sequencing and microarray analysis.

PROCEDURES

1. Highmark Health Options will provide coverage for genetic testing for the following conditions:
    - Hereditary Non-Polyposis Colorectal Cancer (HNPCC [Lynch Syndrome])
    - Familial Adenomatous Polyposis (FAP)
    - Attenuated FAP (AFAP)
    - MYH-associated Polyposis (MAP)

    NOTE: The information from the genetic testing is expected to make an impact on the member's treatment plan or the responsible family member/legal guardian intends to use the information in making decisions about his/her care or treatment plan.

    A. Hereditary Non-Polyposis Colorectal Cancer (HNPCC [Lynch Syndrome])
    Initial comprehensive assessment of a patient for HNPCC must include the collection of family history of cancers, detailed medical and surgical history-including premalignant gastrointestinal conditions, and direct examination for related manifestations. The data collection should provide enough information to develop a preliminary determination of the risk of a familial predisposition to cancer. The age at diagnosis and lineage (maternal and/or paternal) should be documented for all diagnoses, especially in first- and second-degree relatives.

    When indicated, genetic testing for a germline mutation should be done on the patients identified through the family history evaluation and/or tumor analysis to conform a diagnosis and allow for predictive testing of at-risk relatives.

    There are several common findings in families with HNPCC:
        1) The patient has at least three or more relatives who have had colon cancer, endometrial cancer, or another HNPCC related cancer, and at least one of the relatives is a parent, brother, or sister;
        2) Two successive affected generations (i.e., grandparent and a parent);
        3) One of those relatives had colorectal or endometrial cancer before age 50;
        4) Exclusion of familial adenomatous polyposis (FAP)

    The following medical necessity criteria must be met for serum genetic testing for HNPCC (MLH1, MSH2, MSH6, PMS2, EPCAM sequence analysis):
    1) Patients with colorectal cancer, for diagnosing Lynch syndrome (confirmatory testing); OR
    2) The patients without colorectal cancer but with a family history must meet either the *Amsterdam II criteria or revised Bethesda guidelines (confirmatory testing); OR
    3) The patient has had colorectal or endometrial cancer at 50 years of age or younger AND one first-degree relative diagnosed with Lynch-associated cancer, for the diagnosing of Lynch syndrome (confirmatory testing); OR
    4) A first- or second-degree relative with an known HNPCC mutation (genes MLH1, MSH2, MSH6, PMS2, EPCAM/TACSTD1) (predictive testing)
    5) Additional Lynch syndrome (HNPCC) tumor testing are covered when the patient in which a family history has been performed and the patient meets the following medical necessity criteria:
        a. Microsatellite instability (MSI) analysis of tumor cells or immunohistochemical (IHC) analysis of the tumor (colorectal and/or endometrial) when feasible may be considered medically necessary as an initial test in persons with colorectal and/or

endometrial cancer or colorectal adenomas. When malignant tissue is not available from the patient or affected family member, testing can begin on an adenomatous colon polyp. MSI and IHC testing is appropriate for EITHER of the following:

1. Individual with colorectal or endometrial cancer whose family meets the revised Bethesda or Amsterdam II criteria; OR
2. Individual with stage II colorectal cancer for whom adjuvant single-agent fluoropyrimidine chemotherapy is being considered and the testing results will be used in treatment decision making

b. Tumor testing for the BRAF V6OOE and MLH1 promoter hypermethylation is covered for individuals with colon cancer when IHC tumor screening identified a loss of MLH1 expression

c. Genetic testing for EPCAM mutations is considered medically necessary to make a diagnosis of Lynch syndrome in an individual with colorectal or endometrial cancer when:

1. The tumor tissue is negative for MSH2 by IHC and the patient is negative for germline mutation in MSH2; OR
2. Tumor tissue shows a high level of MSI and the patient is negative for a germline mutation in MSH2, MLH1, PMS2 and MSH6; OR
3. At-risk relatives of patients with Lynch syndrome with a known EPCAM mutation; OR
4. Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested or mismatch repair mutations and when sequencing for mismatch repair mutations is negative.

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

Genetic testing to detect mutations in the APC (adenomatous polyposis coli) gene is considered medically necessary for individuals who meet ANY of the following criteria:

1) Individuals with a personal history of equal to or greater than 10 cumulative adenomatous colonic polyps during their lifetime (confirmatory testing) ; OR
2) First- or second-degree relatives of individuals diagnosed with FAP or AFAP (predictive testing); OR
3) First- or second-degree relatives of individuals with known APC gene mutation (predictive testing) ; OR
4) Individuals with a personal history of a desmoid tumor (confirmatory testing)

C. MYH-associated Polyposis (MAP) genetic testing (gene MuY human homolog [MYH])

Genetic testing to detect MYH (known also as MUTYH)-associated polyposis (MAP) is considered medically necessary when ANY of the following criteria are met:

1) The individual has a personal history of equal to or greater than 10 cumulative greater than ten adenomatous colonic polyps (confirmatory testing); OR
2) The individual with autosomal recessive inheritance of MAP phenotype (confirmatory testing); OR
3) The individual is asymptomatic and has a first-degree relative with known MAP mutation (predictive testing)

*Amsterdam II Clinical Criteria

Informational

Three or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis);

All the following criteria must be fulfilled:

1) One should be a first-degree relative of the other two; AND
2) At least two or more successive generations affected ; AND
3) One or more relatives with cancer associated with HNPCC should be diagnosed before the age of 50 years; AND
4) Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma (if any): AND
5) Tumors, if available, should be verified by pathologic examination; AND
6) Modifications:
    a. Very small families, which cannot be further expanded, can be considered to have HNPCC with only two colorectal cancers in first-degree relatives if at least two generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years; OR
    b. In families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with unusual early-onset neoplasm or endometrial cancer is sufficient

D. **Revised Bethesda Guidelines

Informational

The Bethesda guidelines are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also felt to be more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry. The individual must meet ONE of the following criteria:

1) Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50-years old; OR
2) Presence of synchronous (at the same time) or metachronous (at another time, i.e., a recurrence of) CRC or other Lynch syndrome-associated tumors, regardless of age; OR
3) CRC with high microsatellite instability histology (MSI-H) diagnosed in a patient less than 60-years old; OR
4) CRC diagnosed in one or more first-degree relatives with a Lynch syndrome-associated tumor, with one of the cancers being diagnosed at younger than 50 years of age; OR
5) CRC diagnosed with one or more first-degree relatives with an HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous bland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one cancer being diagnosed at younger than age 50 years; OR
6) CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumor, regardless of age

2. Multigene testing panels that include genes associated with colorectal cancer may be useful when more than one gene can explain a patient's clinical and family history. Multigene testing is considered medically necessary when all the individual components have been determined to be appropriate and:

A. The individual has a personal/family history for more than one hereditary cancer syndrome; OR
B. The individual has colonic polyposis with uncertain histology; OR
C. The individual has adenomatous polyposis (specific to APC, MUTYH, POLE, and POLD1); OR
D. The family history does not meet criteria for established testing guidelines BUT there is suspicion of hereditary cancer AND an appropriate genetic testing panel is available; OR
E. Family history is limited or unknown, but the patient has concerns about hereditary cancer; OR
F. The genetic testing panel is used as a second-line testing when the first-line testing is inconclusive.

Documentation requirements:

- Brief explanation of how the results of genetic testing are necessary to guide treatment decisions relevant to the member's personal medical history for positive patient outcome (i.e., whether to perform surgery, determine chemotherapy treatment, choose between medication options, etc.); AND
- Diagnose an illness when signs/symptoms are displayed; OR
- Rule out a diagnosis when signs/symptoms are displayed; OR
- Medical records relevant to the testing being performed are to include:
    - A thorough history and physical examinations by the referring physician; AND
    - Conventional testing and outcomes; AND
    - A three generation pedigree analysis results; AND
    - Conservative treatment provided, if applicable.

The following information is required:

- The specific name of the test or panel; AND
- Name of performing CLIA-accredited laboratory; AND
- The exact gene(s) and/or mutations being testing; AND
- Correct CPT and/or HCPCS code(s); AND
- Estimated cost/quote sheet for the genetic testing panel ordered;

Note:

A. An informed consent must be signed by the patient prior to testing. The consent must include a statement that the patient agrees to post-test counseling and the consent must be made available upon request; AND
B. Pre-test genetic counselling has been performed and post-test genetically counselling by an independent genetic professional is planned.

3. When the genetic testing for colon cancer is not covered
    A. Genetic testing for colon cancer is considered not medically necessary when the criteria listed above are not met because the scientific evidence has not been established.
    B. Colon cancer testing is not typically recommended for children under the age of 18 years because this form of cancer does not develop until adulthood.
    C. More than one multigene testing panel is considered not medically necessary.
    D. In the absence of specific information regarding advances in the knowledge of mutation characteristics for a particular disorder, the current literature indicates that genetic tests for inherited disease only need to be conducted once per lifetime for the member.

4. Post-payment Audit Statement

The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

5. Place of Service
   The place of service for these laboratory services is outpatient.

6. Genetic Counseling
   Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for colorectal cancer mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for colorectal cancer mutation requires documentation of medical necessity from one of the following providers who has evaluated the member and intends to see the person after testing has been performed for counseling:
   A. Board Eligible or Board Certified Genetic Counselor
   B. Advanced Genetics Nurse
   C. Genetic Clinical Nurse
   D. Advanced Practice Nurse in Genetics
   E. Board Eligible or Board Certified Clinical Geneticist
   F. A physician with experience in cancer genetics
   G. A physician specializing in the care for the indication(s) for genetic testing

GOVERNING BODIES APPROVAL

Genetic testing for colorectal cancer susceptibility are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

Additional information available at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

There are tests available in the United States. Cologuard™, developed by Exact Sciences, is currently the only FDA-approved automated fecal DNA testing product (approved August 12, 2014). Cologuard™ analyzes both stool DNA and blood biomarkers. An additional test, ColoSure™, was developed by OncoMethylome, which detects aberrant methylation of the vimentin (hV) gene. This test is offered as a laboratory-developed test, not subject to FDA regulation.

CODING REQUIREMENTS

Procedure Codes

CPT Code	Description
81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated [FAP] gene analysis; full gene sequence

81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated [FAP] gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated [FAP] gene analysis; duplication/deletion variants
81210*	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81288	MHL1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81401	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)
81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

81406	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) when specified as the following: MUTYH (mutY homolog [E.coli]) (e.g., MYH-associated polyposis), full gene sequence
81435	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
81436	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, *and* STK11

*See related GHP medical policy MP-062-MD-PA BRAF

Diagnosis Codes

ICD 10 Codes	**Description**
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.5	Malignant neoplasm of splenic flexure
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.3	Malignant neoplasm of parametrium
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament

C60.1	Malignant neoplasm of glans penis
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
D01.0	Carcinoma in situ of colon
D01.1	Carcinoma in situ of rectosigmoid junction
D01.2	Carcinoma in situ of rectum
D12.0	Benign neoplasm of cecum
D12.1	Benign neoplasm of appendix
D12.2	Benign neoplasm of ascending colon
D12.3	Benign neoplasm of transverse colon
D12.4	Benign neoplasm of descending colon
D12.5	Benign neoplasm of sigmoid colon
D12.6	Benign neoplasm of colon, unspecified
D12.7	Benign neoplasm of rectosigmoid junction
D12.8	Benign neoplasm of rectum
D12.9	Benign neoplasm of anus and anal canal
D23.0	Other benign neoplasm of skin of lip
D23.10	Other benign neoplasm of skin of unspecified eyelid, including canthus
D23.11	Other benign neoplasm of skin of right eyelid, including canthus
D23.12	Other benign neoplasm of skin of left eyelid, including canthus
D23.20	Other benign neoplasm of skin of unspecified ear and external auricular canal
D23.21	Other benign neoplasm of skin of right ear and external auricular canal
D23.22	Other benign neoplasm of skin of left ear and external auricular canal
D23.30	Other benign neoplasm of skin of unspecified part of face
D23.39	Other benign neoplasm of skin of other parts of face
D23.4	Other benign neoplasm of skin of scalp and neck
D23.5	Other benign neoplasm of skin of trunk
D23.60	Other benign neoplasm of skin of unspecified upper limb, including shoulder
D23.61	Other benign neoplasm of skin of right upper limb, including shoulder
D23.62	Other benign neoplasm of skin of left upper limb, including shoulder
D23.70	Other benign neoplasm of skin of unspecified lower limb, including hip
D23.71	Other benign neoplasm of skin of right lower limb, including hip
D23.72	Other benign neoplasm of skin of left lower limb, including hip
D23.9	Other benign neoplasm of skin
D37.4	Neoplasm of uncertain behavior of colon
D37.5	Neoplasm of uncertain behavior of rectum
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue [desmoid tumor]
D49.0	Neoplasm of unspecified behavior of digestive system
K63.5	Polyp of colon

L85.8	Other specified epidermal thickening [keratoacanthoma]
Z80.0	Family history of malignant neoplasm of digestive organs
Z80.41	Family history of malignant neoplasm of ovary
Z80.49	Family history of neoplasm of other genital organs
Z80.51	Family history of malignant neoplasm of kidney
Z80.59	Family history of malignant neoplasm of other urinary tract organ
Z80.8	Family history of malignant neoplasm of other organs or systems
Z83.71	Family history of colonic polyps
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z86.010	Personal history of colonic polyps
Z87.39	Personal history of other diseases of musculoskeletal system and connective tissue (desmoid tumor)

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

Hereditary Non-Polyposis Colon Cancer, Familial Adenomatous Polyposis, Attenuated Familiar Adenomatous Polyposis and MYH-associated Polyposis

There are multiple well-defined types of hereditary colorectal cancer; three of the most common are familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC) and MYH-associated Polyposis (MAP). FAP can be clinically recognized by the presence of hundreds of colon polyps, typically apparent by age 10-20. If left untreated, affected individuals will go on to develop colorectal cancer. Individuals with HNPCC tend to have early-onset colorectal cancer, right-sided tumors and/or multiple synchronous or metachronous lesions. Extracolonic tumors may also be present. The lifetime risk of developing colorectal cancer in HPNCC is approximately 80%. Lynch syndrome is associated with a risk of developing colorectal cancer by age 70 years of approximately 27% to 45% for men, and 22% to 38% for women, after correction for ascertainment bias. Germline mutations have been associated with both FAP and HNPCC creating the option of genetic testing of both affected individuals (to establish the genetic basis of the tumor) and their family members (to determine whether an individual carries the same mutation as the affected relative). Individuals with germline mutations may undergo increased surveillance or may consider prophylactic colectomy.

For hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, germline testing may be used to identify mismatch repair (MMR) gene mutations. A blood sample is taken to identify mutations by sequence, deletion, duplication analysis, or rearrangement analysis. However, genetic testing for mutations in DNA MMR genes is expensive and time-consuming. Therefore, researchers have proposed techniques to identify ideal candidates (patients with cancer who are most likely to be HNPCC carriers). The Amsterdam criteria are useful but do not identify up to 30% of potential Lynch syndrome carriers.

Researchers have combined microsatellite instability (MSI) profiling and immunohistochemistry (IHC) tumor testing for DNA MMR gene expression. They identified an additional 32% of Lynch syndrome carriers that MSI profiling alone would have missed. Currently, this combined MSI profiling and IHC testing strategy is the most advanced method of identifying candidates for genetic testing for Lynch syndrome.

The next step would be to consider performing a blood test to assess for HNPCC or Lynch syndrome genetic mutation.

Genetic testing is not necessary to establish a diagnosis of HNPCC or Lynch syndrome and does not provide a definitive diagnosis. The decision to go forward with genetic testing is complex. Patients should consult a genetic specialist, such as a genetic counselor, to discuss the benefits and risks before undergoing genetic testing.

Some mutations in the EPCAM gene are associated with Lynch syndrome. The EPCAM gene lies next to the MSH2 gene and provides instructions for making an individual messenger RNA (mRNA), which serves as the genetic blueprint for making the protein. EPCAM gene mutations cause the MSH2 gene to become inactivated by a mechanism known as promoter hypermethylation. The MSH2 protein is crucial in repairing mistakes in DNA. Loss of this protein prevents proper DNA repair and may result in uncontrolled cell growth and an increased risk of cancer.

MAP is an autosomal recessive form of FAP that increases the individual's risk of developing attenuated adenomatous polyposis and colorectal cancer. There may also be an increased risk of polyps in the duodenum, although the incidence of duodenal polyposis is reported less frequently than in FAP. The magnitude of the risk of duodenal cancer has not yet been defined. As in the case of FAP, some individuals with MYH mutations may require colectomy, but the procedure is usually done at a later age than those with FAP.

Genetic Testing With Gene Panels

Next-generation sequencing addresses any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. Next-generation sequencing is not a specific sequencing technology or a test in itself. Instead, the term emphasizes the difference between the earlier testing methods that involved the sequencing of one DNA strand at a time. Next-generation sequencing includes but is not limited to massively parallel sequencing and microarray analysis.

According to the 2018 NCCN Guidelines, multigene testing has altered the clinicians approach to testing at-risk patients and their families. Panel testing is most beneficial when one or more genes will explain a patient's clinical history. While panel testing has the potential benefit of analyzing multiple genes, the dilemma on limited data and lack of clear guidelines on cancer risk and management of risk for carriers of these genes remain. In addition, the panel results may detect genetic mutations of uncertain clinical significance and multigene panel components may vary among those that are commercially available. NCCN supports the use of multigene testing panels in various circumstances but notes that caution should be used when recommending multigene testing and that additional guidance is needed on the management of results.

POLICY SOURCE(S)

Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. Feb 18 2004; 96(4):261-268. PMID 14970275. Accessed on February 16, 2017.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colon Cancer, v 1.2016. Accessed May 6, 2016.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening, v 1.2015. Accessed on May 6, 2016.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Uterine Neoplasms, v 1.2016. Accessed on May 6, 2016.

Pennsylvania Department of Human Services. Technology Assessment Group Coverage Decisions. Managed Care Operations Memorandum. MC OPS #HCALL-07/2005-015. Accessed on May 9, 2016.

Pennsylvania Department of Human Services. Technology Assessment Group Coverage Decisions. Managed Care Operations Memorandum. MCOPS Memo # 03/2015-001. Accessed on May 26, 2016.

National Comprehensive Cancer Network® (NCCN). Clinical practice guidelines in oncology. Colorectal screening. Version 1.2010. Accessed on May 24, 2016.

Imperiale, TF, Ransohoff, DF, Itzkowitz, SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014 Apr 3; 370(14):1287-97. PMID: 24645800. Accessed on May 24, 2016.

Lin, JS, Webber, EM, Beil, TL, Goddard, KA, Whitlock, EP. Lin JS, Webber EM, Beil TL, Goddard KA, Whitlock EP. Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. PMID: 22457883. [Book] 2012 Feb [cited 07/2015]; 2012/03/30: Accessed on May 24, 2016.

National Library of Medicine (NLM). Genetics Home Reference. EPCAM. Reviewed May 2013. Accessed on May 24, 2016.

American Cancer Society. Accessed on June 2, 2016.

Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. *J Natl Cancer Inst*. 1997 Dec 3. 89(23):1758-62. Accessed on May 24, 2016.

Policy History

Date	Activity
09/06/2016	QI/UM Committee approval
12/15/2016	Provider effective date
02/08/2017	Revisions: General formatting changes; Page 1-Added Related Policy Number & Effective; Page 3-added statement on impact of testing results on treatment plans; Page 14-corrected typographical error; Pg. 2 Rearranged the attachments; Highmark Health Options disclaimer update on external document
03/14/2017	QI/UM Committee Review Approval
08/09/2017	Revisions: Issue Date added to opening policy box; Procedure and Diagnosis code tables retitled to 'Covered'. Amsterdam & Bethesda Guidelines are informational. Fecal DNA testing language and procedure code 81528 removed from policy; refer to new medical policy MP-059-MD-WV.
09/27/2017	QI/UM Committee Review
11/01/2017	Revised Provider effective date
04/25/2018	Revision: Removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C
08/01/2018	Annual Review: Added MP-062-MD-PA as new related medical policy in title box; updated CPT description of 81435 & 81436; Added procedure 81210 as covered code in Attachment B; Revised Summary of Literature with the removal of fecal DNA testing as not appropriate for this policy; Updated Summary of Literature; Removed all reference article direct links in the Reference section and updated NCCN reference.
09/11/2018	QI/UM Committee Review Approval
11/15/2018	Provider effective date

/KP