CLINICAL MEDICAL POLICY	
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Page Number(s):	1 of 12

DISCLAIMER

Gateway Health℠ (Gateway) 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

Gateway Health℠ provides coverage under the LABORATORY medical-surgical benefits of the Company's Medicare 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.

DEFINITIONS

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, or 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 instructions 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 as 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. Gateway Health℠ 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 the member's 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 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); OR
5) Additional Lynch syndrome (HNPCC) tumor-testing is 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 are 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 greater than ten 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 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)

D. *<u>Amsterdam II Clinical Criteria</u>
Three or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis). All of 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

E. **<u>Revised Bethesda Guidelines</u>
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. When the genetic testing for colon cancer susceptibility 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. Genetic testing for colorectal cancer susceptibility using panels of genes (with or without next-generation sequencing) are considered not medically necessary. This includes but is not limited to ColoNext™. Note: individual components of a panel may be considered medically necessary when criteria are met.
   C. 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.

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

4. 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 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 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 regulations.

Coverage Determination
Gateway Health ℠ follows the coverage determinations made by CMS as outlined in either the national coverage determinations (NCD) or the state-specific local carrier determination (LCD).

For North Carolina, please use the following link for Palmetto GBA LLC, Inc. list of LCDs:
https://www.cms.gov/medicare-coverage-database/indexes/lcd-list.aspx?Cntrctr=381&name=&DocType=Active&ContrVer=1&CntrctrSelected=381*1&s=34%7c48%7c53%7c58&bc=AggAAAQAAAAAAA%3d%3d&#ResultsAnchor

CODING REQUIREMENTS

Covered Procedure Codes

CPT Codes	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
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

Covered 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 Gateway Health℠ 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.

Next-generation sequencing has led to the development of genetic testing incorporating panels which analyze multiple genes for multiple mutations simultaneously. Researchers are investigating genetic testing using panels of genes as a means to identify genetic mutations that may contribute to the development of hereditary cancers. Various laboratories have begun to offer next-generation sequencing panels. The ColoNext™ test (manufactured by Ambry Genetics) is one such example, that tests for variants in 14 genes that have been associated with hereditary CRC, including the genes that cause Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM) as well as the gene that causes FAP (APC).

Fecal DNA Testing

In 2012, the AHRQ published a comparative effectiveness review of fecal DNA testing for colorectal cancer risk in average-risk adults. Following an extensive review of the literature, the researchers identified only three studies of diagnostic accuracy in screening populations (versus populations with known colorectal cancer status), which reported low sensitivities (25% to 56%) for the detection of colorectal cancer, and similarly low sensitivities for the detection of advanced adenomas (11% to 39%). The researchers point out that results of these publications are specific to tests no longer on the U.S. market (such as the PreGen-Plus test) and that these results may not be applicable to the use of the ColoSure test. The review concluded that despite considerable media attention and expert-based clinical recommendations that include fecal DNA testing for CRC screening, at present, fecal DNA tests have insufficient evidence about their clinical validity (diagnostic accuracy) in patients at average risk for CRC.

A study by Imperiale et al. (2014) reported on the evaluation of DNA testing in the detection of colorectal cancer and the performance of the DNA test as compared to commercially available fecal immunochemical testing. The authors concluded that while the use of stool DNA testing significantly detected more cancers than fecal immunochemical testing, there were more false positives in asymptomatic persons at average risk for colon cancer.

The National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer screening note that stool DNA testing is not considered a primary screening modality (NCCN 2015). The guidelines indicate more research is needed to determine an appropriate interval between screenings.

POLICY SOURCE(S)

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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 and available at: https://dpwintra.dpw.state.pa.us/HealthChoices/custom/post/mcopsmemo/mcopsmemo.asp.

Policy History

Date	Activity
08/08/2017	Initial policy developed
08/16/2017	QI/UM Committee approval
10/01/2017	Provider effective date