Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MP098

Section: Medical Benefit Policy

Subject: Genetic Testing Related to Colorectal Cancer

I. Policy: Genetic Testing Related to Colorectal Cancer

II. Purpose/Objective:

To provide a policy of coverage regarding Genetic Testing Related to Colorectal Cancer

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

(i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
(ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
(iii) The service or benefit will assist the Member to achieve or maintain maximum functional

capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.

DESCRIPTION:
Genetic testing involves the analysis of DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes. There are currently two well-defined types of hereditary colorectal cancer, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).

INDICATIONS:

***REQUIRES PRIOR MEDICAL DIRECTOR or DESIGNEE AUTHORIZATION**

- Genetic testing to determine the carrier status of the adenosis polyposis coli (APC) gene when criteria are met. (See applicable medical criteria below)
- Genetic testing to determine the carrier status of the MutY homolog [MYH] when the member meets criteria (*See applicable medical criteria below)
- Lynch Syndrome - Genetic testing to determine the carrier status of the HNPCC associated genes when either the Amsterdam or Bethesda criteria is met. (*See applicable medical criteria below)

MEDICAL CRITERIA:

For APC gene testing for familial adenomatous polyposis (FAP) and Attenuated FAP (AFAP):

To determine carrier status of the adenomatous polyposis coli gene (APC) for familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP) in the following subjects:

1. Individuals with greater than 10 adenomatous colonic polyps in their lifetime; OR
2. In first-degree relatives (e.g., siblings, parents, offspring) of an individual diagnosed with FAP or AFAP; OR
3. Personal history of desmoid tumor, hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer

For MutY human homolog [MYH]) gene testing for MYH-associated polyposis (MAP) :

MYH-associated polyposis (MAP) genetic testing (gene MutY human homolog [MYH]) is covered in ANY of the following situations:

- Confirmatory testing for individuals with a history of adenomatous polyposis (>10 adenomas) and negative APC mutation testing: **or**
- For predictive testing when an individual has a first-degree relative with known MYH polyposis; **or**
- For predictive testing when an individual has at least one first-degree relative affected with findings consistent with recessive inheritance (i.e., MAP)

Lynch Syndrome:

For HNPCC; Lynch Syndrome genetic testing (gene MLH1, MSH2, MSH6, PMS2, EPCAM):

NOTE: COLARIS Test® is a patented test for assessment of colorectal cancer risk. It detects mutations in MLH1, MSH2, PMS2 and EPCAM genes. COLARIS AP detects mutations in the APC and MYH genes.

Hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome (LS): (MLH1, MSH2, MSH6, PMS2, EPCAM sequence analysis) gene testing is considered medically necessary for members who meet any one of the following criteria:
The member:

- is diagnosed with colorectal cancer with the MSI histology at any age; *or*
- is diagnosed with endometrial cancer before age 50 years; *or*
- meets Amsterdam or Revised Bethesda Guidelines; *or*
- has a personal history of colorectal or endometrial cancer and the tumor shows evidence of mismatch repair deficiency (either high microsatellite instability [MSI] or loss of mismatch repair protein expression) at any age; or
- is diagnosed with a synchronous, or metachronous Lynch Syndrome (LS)-associated tumors*, regardless of age; or
- has a 1st- or 2nd-degree relative with a disease confirmed to be caused by a HNPCC mutation (genes MLH1, MSH2, MSH6, PMS2, EPCAM); *or*
- has ≥5% risk of LS on a validated mutation prediction model (eg, MMRpro, PREMM, MMRpredict)
    - http://premm.dfci.harvard.edu/
    - http://hnpccpredict.hgu.mrc.ac.uk/.
    - http://www4.utsouthwestern.edu/breasthealth/cagene/.

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

Amsterdam II Criteria	Revised Bethesda Guidelines
Three or more relatives with a cancer associated with Lynch syndrome (cancer of the colorectum, endometrium, small bowel, ureter, or renal pelvis) and ALL of the following: • **One must be a first-degree relative of the other two; AND** • **Two or more successive generations must be affected; AND** • **One or more relatives should be diagnosed before age 50 years; AND** • **Familial adenomatous polyposis (FAP) should be excluded in colorectal cancer (CRC) cases;** **AND** • **Tumors should be verified by pathologic examination.**	**Tumors from individuals should be tested for MSI in the following situations:** • **Colorectal cancer diagnosed in a patient who is less than 50 years of age.** • **Presence of synchronous, metachronous colorectal, or other LS-related tumors,* regardless of age.** • **Colorectal cancer with the MSI-H histology diagnosed in a patient who is less than 60 years of age.** • **Colorectal cancer diagnosed in one or more first-degree relatives with an LS-related tumor, with one of the cancers being diagnosed under age 50 years.** • **Colorectal cancer diagnosed in two or more first- or second-degree relatives with LS-related tumors, regardless of age.**

* Lynch syndrome-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas.

Microsatellite instability (MSI) Testing or immunohistochemical (IHC) Analysis

Microsatellite instability (MSI) testing or immunohistochemical (IHC) analysis of the tumor is considered medically necessary when any of the following criteria are met:

- all members with colorectal cancer regardless of age; or
- members with endometrial cancer; or

For members with unresectable or metastatic solid tumors, either MSI or IHC or a multigene NGS or other multi-analyte methodology panel inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes is medically reasonable and necessary.

MSI testing or IHC analysis should be used as an initial test in members with colorectal or endometrial cancer to identify those who should proceed with HNPCC mutation analysis.

*__NCCN Guidelines v1.2021 Lynch Syndrome__: the panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab-based universal screening. If tumor is available, LS-specific testing or multi-gene testing without IHC or MSI should be utilized in select cases under direction of a clinician with expertise in genetics, and should not be used as a universal screening strategy.

BRAF V600E OR MLH1 PROMOTER METHYLATION

Genetic testing for BRAF V600E or MLH1 promoter methylation is considered medically necessary to rule out a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a CRC tumor on immunohistochemical (IHC) analysis.

SMAD4 AND BMPR1A TESTING (Juvenile Polyposis Syndrome)

Genetic testing for SMAD4 and BMPR1A gene variants is considered medically necessary when any one of the following criteria is met:

1. A documented diagnosis of juvenile polyposis syndrome based on any one of the following:
   - at least 3 juvenile polyps in the colon; or
   - multiple juvenile polyps in other parts of the gastrointestinal tract; or
   - any juvenile polyps in a person with a known family history of juvenile polyps

OR

2. Documentation of a relative diagnosed with juvenile polyposis syndrome.

STK11 Testing (Peutz-Jeghers Syndrome)

Genetic testing for STK11 gene variants is considered medically necessary when any of the following criteria is met:
There is a known family history of STK11 (LKB1) gene mutation; or
The member has a clinical diagnosis of PJS based on as least TWO of the following features:

- Two or more histologically confirmed Peutz-Jeghers polyps of the small intestine
- characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
- family history of Peutz-Jeghers syndrome

COLOGUARD TESTING:

Fecal DNA Testing: (e.g., Cologuard,) **DOES NOT REQUIRE PRIOR AUTHORIZATION** a noninvasive, multitarget fecal DNA test for the qualitative detection of colorectal neoplasia-associated DNA markers in addition to the presence of occult hemoglobin in stool is covered as a preventive screening methodology once every 3 years according to the following criteria:

- Age 45 to 85 years; and
- Asymptomatic (no signs/symptoms including but not limited to, lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test, or fecal immunochemical test); and
- There has been no documentation of a normal colonoscopy in the previous 10 years; and
- At average risk of developing CRC defined as:
    - no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease including Crohn's disease and ulcerative colitis; and
    - no family history of colorectal cancer or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis CRC

Genetic testing is appropriate only when offered in a setting where a licensed or certified genetic counselor* or adequately trained health care professional is able to provide appropriate pre- and post-test genetic counseling, and medical necessity is supported by ALL of the following criteria:

1. The information is needed to adequately assess risk; and
2. The information will be used in the immediate care plan; and
3. Pedigree analysis establishes a high risk group for the disease; or
4. Clinical presentation of symptomology is evident and diagnosis cannot be established with conventional evaluation testing.

*A genetic counselor is considered by the Plan to be qualified if the following are met:

- M.S. or Ph.D. degree from a genetic counseling program approved/recognized by the American Board of Genetic Counseling or the American Board of Medical Genetics.

or

- Board certified or board qualified/eligible in the orderly process of obtaining board certification by the American Board of Genetic Counseling or American Board of Medical Genetics

and

- Proof of current competence and demonstrated ability (minimum of two years recent and continual experience within the past three years).

EXCLUSIONS:
There is no evidence to support the use of genetic testing for individuals from the general population with average risk. This is considered **NOT MEDICALLY NECESSARY.**

The ColonSentry testing panel is considered **experimental, investigational, or unproven** and **is NOT COVERED.** There are no current evidence-based guidelines from medical professional organizations or public health agencies that recommend ColonSentry for colorectal cancer screening and no evidence to support the use of this testing.

For Commercial and Medicaid Business Segments: The Epi proColon test is considered **experimental, investigational, or unproven** and is **NOT COVERED**. The Geisinger Technology Assessment Committee evaluated this technology and concluded that there is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

For Medicare Business Segment: Epi proColon testing is covered as an alternative colorectal cancer screening strategy.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

PROCESS:
The Plan will utilize available published, peer reviewed medical literature, independent technology assessment program reports and/or review by the Geisinger Clinic Technology Assessment Committee to evaluate the following criteria when assessing the validity and efficacy of a specific genetic test:

- The analytical power of a test determined by its sensitivity and specificity is established.
- There is evidence of defined outcome measures that permits conclusions concerning the effect on health outcomes.
- The net health outcomes benefit of the test as compared to established alternatives is evaluated if applicable.
- The availability of test to membership is evaluated.
- The appropriate governmental and/or professional regulatory body approval is established.
- The test result will influence the treatment or alter the management of the member medical care plan.
- The test result has the capability to confirm a diagnosis when conventional medical evaluation is equivocal.

CODING ASSOCIATED WITH: Genetic Testing Related to Colorectal Cancer
The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov ***or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.***

81201 APC (ADENOMATOUS POLYPOSIS COLI) (EG, FAMILIAL ADENOMATOSIS POLYPOSIS [FAP], ATTENUATED FAP) GENE ANALYSIS; FULL GENE SEQUENCE
81202 APC (ADENOMATOUS POLYPOSIS COLI) (EG, FAMILIAL ADENOMATOSIS POLYPOSIS [FAP], ATTENUATED FAP) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS
81203 APC (ADENOMATOUS POLYPOSIS COLI) (EG, FAMILIAL ADENOMATOSIS POLYPOSIS [FAP], ATTENUATED FAP) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS
81288 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81435 Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include analysis of at least 7 genes, including APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, and PMS2
81436 Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatosis polyposis); duplication/deletion gene analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, and MUTYH
81525 ONCOLOGY (COLON), MRNA, GENE EXPRESSION PROFILING BY REAL-TIME RT-PCR OF 12 GENES (7 CONTENT AND 5 HOUSEKEEPING), UTILIZING FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE, ALGORITHM REPORTED AS A RECURRENCE SCORE
81528 Fecal DNA Test- Cologuard
81210 BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81309 PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha)(eg. colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7,9, 20)
81317 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81327 Sept9 (septin 9) (eg, colorectal cancer) methylation analysis
0101U Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrom, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sangar, MLPA, and array CGH, with MRNA analytics to resolve v
0155U (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha)(eg. colorectal and breast cancer) gene analysis,
0157U APC (APC regulator of WNT signaling pathway)(EG,familial adenomatosis polyposis [FAP] MRNA sequence analysis (list seperately in addition to code for primary procedure
0158U MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0159U MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0160U MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0161U PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis
0162U Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2)
0163U Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas (new code effective 4/1/20) (BeScreened™-CRC)
0235U 0235U PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
0238U Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
0261U Oncology (colorectal cancer), image analysis with artificial intelligence assessment of 4 histologic and immunohistochemical features (CD3 and CD8 within tumor-stroma border and tumor core), tissue, reported as immune response and recurrence-risk score (Immunoscore®)

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

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This policy will be revised as necessary and reviewed no less than annually.

Devised: 6/03

Revised: 7/23/04(criteria); 6/05 (update Bethesda criteria); 6/06; 6/07(revised criteria); 6/09 (coding); 6/10 (updated criteria); 8/12, 11/14 (Added medicare, Medicaid, healthy PA for Fecal DNA), 11/15 (added exclusion); 5/16 (expanded coverage for fecal DNA testing); 11/16 (remove PA for fecal DNA screening test); 4/17 (clarified criteria), 4/18 (criteria update); 7/19 (add Medicare Epi proColon coverage), 11/19 (update Cologuard age recommendation); 11/20 (add gene variants and criteria), 11/21 (revise Lynch, IHC and MSI criteria)

Reviewed: 7/08, 1/11, 1/12, 8/13, 8/14, 4/19