CLINICAL MEDICAL POLICY	
Policy Name:	Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
Policy Number:	MP-018-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	10/01/2024; 10/01/2023; 10/01/2022; 12/17/2021; 10/19/2020;11/18/2019; 11/15/2018; 09/15/2017
Effective Date:	11/01/2024;11/01/2023; 11/01/2022; 01/17/2022; 11/16/2020;11/18/2019; 11/15/2018; 09/15/2017
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Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 16

Policy History

Date	Activity
11/01/2024	Provider Effective date
09/09/2024	PARP Approval
08/21/2024	QI/UM Committee review
08/21/2024	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections. Updated the code Description for the following Procedure Codes: 81401 ,81403 , 81405 , & 81406.
11/01/2023	Provider Effective date
09/22/2023	PARP Approval
08/16/2023	QI/UM Committee review
08/16/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
11/01/2022	Provider Effective date
09/12/2022	PARP Approval
08/17/2022	QI/UM Committee review
08/17/2022	Annual Review: No changes to clinical criteria. Reformatted 'Procedures' section numbering & wording. Updated the 'Summary of Literature' and 'Reference Sources' sections. Removed the following 'unspecified' ICD-10 codes: C57.00, C57.10, C57.20,

	C65.9, D01.40, D23.20, D23.30, D23.60, & D23.70. Removed incorrect TAG determination on CPT code 81401, this code does not require a Program Exception.
01/17/2022	Provider effective date
11/30/2021	PARP Approval
08/18/2021	QI/UM Committee review
08/18/2021	Annual Review: Updated Summary of Literature and Reference sections. Reviewed criteria as well as coding against most recent guidelines.
11/16/2020	Provider Effective Date
09/21/2020	PARP Approval
08/19/2020	QI/UM Committee review
08/19/2020	Annual Review: Revised medical necessity statement in section 1 to say, “in any of the following situations when." Revised title of policy to reflect policy contents; Revised medical necessity statement in section 1 to say, “in any of the following situations when." Added “OR” to section A, 3, H, iii. Changed “OR” to ‘AND in section C, 1. Added “AND” to section C2. Revised medical necessity statement in C, 3 to say “The patients meeting any of the following criteria…” Added definition for CHRPE, formatting changes; updated the Summary of Literature and Reference sections; added CPT codes 81405, 0101U & 0130U.
11/18/2019	Provider effective date
10/15/2019	PARP Approval
08/21/2019	QI/UM Committee Review
07/12/2019	Annual Review: Removed the definitions for genetic testing & counseling & added definition for LS-related cancers; under Procedures, all criteria sets were reformatted and updated; Moved the Amsterdam and Bethesda guidelines to the Summary of Literature sections as the guidelines were included in each of the criteria sets; added ICD-10 diagnosis codes C16.0-C16.9, C20, C21.0-C21.8, C23, C24.0-C24.9, C25.0, C25.3-C25.9, C54.0-C54.9 and C65.1-C65.9, D01.40 and D01.49.

Disclaimer

Highmark Wholecare℠ 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 Wholecare℠ 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.

(Current applicable PA HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.

Definitions

Prior Authorization Review Panel (PARP) – A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

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.

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 (Lynch syndrome) (LS) – An inherited colorectal cancer syndrome that accounts for 5% to 8% of all colorectal cancers.

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, grandchild, 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.

Lynch Syndrome Related Cancer - Lynch syndrome related tumors that include: gastric, small bowel, colorectal, endometrial, ovarian, pancreas, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas, and ker-acanthomas.

MYH-Associated Neoplasia - An autosomal recessive condition that is the result of defects in the MUTYH homolog genes.

Serrated Polyposis Syndrome - A condition that is comprised of multiple colorectal serrated polys (hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas). There appears to be a familial component to this condition, but the genetic basis remains unknown.

Congenital Hypertrophy or Hyperplasia of the Retinal Epithelium (CHRPE) - A rare benign lesions of the retina that are the result of a congenital proliferation of pigmented epithelial cells which appear as round or oval lesions in the fundus grouped together as resembling 'bear tracks'.

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

Procedures

1. Highmark Wholecare℠ considers genetic testing medically necessary for ANY of the following conditions:
    A. **Hereditary Non-Polyposis Colorectal Cancer (Lynch Syndrome, LS)**
    Genetic testing (MLH1, MSH2, MSH6, PMS2, or EPCAM sequence analysis) for LS may be considered medically necessary in ANY of the following situations:
        1) When the information that may guide the targeted testing is available, AND one of more of the following are met:
            a. Immunohistochemical (IHC) shows loss of nuclear staining for one (1) or more of the mismatch repair enzymes (MMR) and gene testing is guided by these results; OR
            b. The individual has a family history of a known mutation in MLH1, MSH2, MSH6, PMS2, or EPCAM; OR
            c. The test results will result in clinical management decisions; OR
        2) When the information that may guide targeted testing is unavailable, AND one of more of the following are met:
            a. There are no IHC tumor testing results; OR
            b. There is no family history of a known mutation in MLH1, MSH2, MSH6, PMS2, or EPCAM genes; OR
            c. The affected family member is unavailable for testing; OR
            d. The individual has a colorectal or endometrial cancer diagnosed before age 50; OR
            e. The individual has colorectal or endometrial cancer diagnosed at any age when there is a family history of a 1st or 2nd degree relative with LS-related cancer diagnosed prior to age 50; OR
            f. The individual has colorectal or endometrial cancer diagnosed at any age when there is a family history of two or more 1st or 2nd degree relatives with LS-related cancer diagnosed at any age; OR
            g. The individual has a personal history of synchronous or metachronous LS-related tumor(s) diagnosed at any age; OR
            h. The individual has a personal history of colorectal or endometrial cancer, and the tumor shows evidence of mismatch repair deficiency (high microsatellite or loss of mismatch repair protein expression) at any age; AND
                i. The individual has a predicted risk for LS greater than 5% on one of the prediction models (e.g., MMRpro, PREMM, or MMRpredict); OR

ii. The individual obtaining the testing has a 1st degree relative with two or more LS-related tumors, including synchronous and metachronous tumors; OR
iii. The individual obtaining the testing has a family history of three or more 1st or 2nd degree relatives with LS-related cancers, regardless of age; OR
iv. The individual meets the Amsterdam or Revised Bethesda Guidelines; OR

3) The individual has been previously diagnosed with colorectal and/or endometrial cancer and has mismatch repair (MMR) deficiency, either by microsatellite instability (MSI) or IHC; OR

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

Genetic testing to detect mutations in the APC gene may be considered medically necessary when ALL of the following are met:

1) individual has at least 20 cumulative adenomatous colonic polyps during their lifetime; OR
2) 1st or 2nd degree relatives have been diagnosed with FAP or AFAP; OR
3) 1st or 2nd degree relatives have a known APC gene mutation; OR
4) Individuals with personal history of desmoid tumor, hepatoblastoma, cribriform morular variant of papillary thyroid cancer or multifocal CHRPE; OR

C. **MUTYH-Associated Polyposis (MAP)**

Genetic testing for MAP may be considered medically necessary when ALL of the following criteria are met:

1) The individual has had greater than 10 adenomatous colonic polyps; AND
2) The individual is asymptomatic and has a 1st degree relative with known MAP mutation; AND
3) The individuals meets ANY of the following criteria for serrated polyposis syndrome (SPS):
    a. The individual has at least 5 serrated polyps proximal to the sigmoid colon with 2 or more of these being greater than 10mm; OR
    b. Any number of serrated polyps proximal to the sigmoid colon in an individual who has a 1st degree relative with serrated polyps; OR
    c. Greater than 20 serrated polyps of any size but distributed throughout the colon.

2. **Epithelial Cellular Adhesion Molecule Gene (EPCAM)**

Genetic testing for EPCAM mutations may be considered medically necessary to make a diagnosis of LS in an individual with colorectal or endometrial cancer when ANY of the following criteria are met:

A. The tumor tissue is negative for MSH2 by IHC, and the individual is negative for germline mutation in MSH2; OR
B. Tumor tissue shows a high level of MSI, and the individual is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6; OR
C. At-risk relatives of individuals with LS with a known EPCAM mutation; OR
D. Individuals without colorectal cancer, but with a family history meeting the Amsterdam II or Revised Bethesda criteria, when no affected family members have been tested for mismatch repair mutations, and when sequencing for mismatch repair mutations is negative.

3. 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 may be

considered medically necessary when all of the individual components of the panel have been determined to be appropriate and ANY of the following criteria are met:

A. The individual has colonic polyposis with uncertain histology; OR
B. The individual has adenomatous polyposis (specific to APC, MUTYH, POLE, and POLD1); OR
C. 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
D. Family history is limited or unknown, but the patient has concerns about hereditary cancer; OR
E. The genetic testing panel is used as a second-line testing when the first-line testing is inconclusive.

4. Medical records relevant to the genetic testing being performed should include ALL of the following documentation requirements:
    A. A brief explanation of how the results of genetic testing are necessary to guide treatment decisions relevant to the individual's personal medical history for positive patient outcome (i.e., whether to perform surgery, determine chemotherapy treatment, choose between medication options, etc.); AND
    B. A thorough history and physical examination by the referring physician; AND
    C. Previously performed conventional and conservative testing and outcomes; AND
    D. Three-generation pedigree analysis results; AND
    E. 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.
    F. The specific name of the test or panel; AND
    G. Name of performing CLIA-accredited laboratory; AND
    H. The exact gene(s) and/or mutations being testing; AND
    I. Estimated cost/quote sheet for the genetic testing panel ordered; AND
    J. Documentation the pre-test genetic counseling has been performed, and post-test genetically counseling by an independent genetic professional is planned.

5. Genetic testing for colon cancer susceptibility is not considered medically necessary under the following conditions:
    - When the criteria listed above is not met, because the scientific evidence has not been established
    - Colon cancer testing is not typically recommended for children under the age of 18 years because this form of cancer usually does not develop until adulthood.
    - More than one multigene testing panel is considered not medically necessary.
    - 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 patient.

6. Place of Service
    The proper place of service for colorectal cancer genetic testing is in the outpatient setting.

7. Genetic Counseling
    Pre- and post-test genetic counseling is required to be performed by an independent genetic provider (not employed by a genetic testing lab) prior to genetic testing for mutations. This service is necessary in order to inform patient being tested about the benefits and limitations of specific genetic tests. Genetic testing for mutations requires documentation of medical necessity from at

least one of the following providers who has previously evaluated the patient, and intends to see the patient after genetic testing has been performed:

- Board Eligible or Board Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetics
- Board Eligible or Board Certified Clinical Geneticist
- A physician of appropriate expertise or other obstetrical provider specializing in the care for the indication(s) for genetic testing

8. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

9. Related Policies
   - MP-062-MD-PA BRAF Mutation Analysis
   - MP-059-MD-PA Colorectal Cancer Screening

Governing Bodies Approval

Genetic testing for colorectal cancer susceptibility is 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.

Summary of Literature

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2020, an estimated 104,610 new cases of colon cancer and 43,340 cases of rectal cancer will occur. During the same year, an estimated 53,200 people will die of colon and rectal cancer combined. Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005 and, more recently, 38.7 in 2016. In addition, mortality from CRC has been decreasing for decades (since 1947 in women and since 1980 in men) and is currently down by more than 50% from peak mortality rates (NCCN, 2023).

The most common type of colorectal cancer is adenocarcinoma. Adenocarcinomas of the colon and rectum make up 95 percent of all colorectal cancer cases. In the gastrointestinal tract, rectal and colon adenocarcinomas develop in the cells of the lining inside the large intestine. These adenocarcinomas typically start as a growth of tissue called a polyp. A particular type of polyp called an adenoma may develop into cancer. Polyps are often removed during a routine colonoscopy before they may turn cancerous (Markman, 2022).

Familial adenomatous polyposis (FAP) accounts for about 1 percent of all cancers in the colon or rectum. Individuals with this syndrome may develop hundreds or even thousands of colon or rectal polyps. These

polyps tend to occur when individuals with this syndrome are 10 to 12 years old. Nearly all people with FAP develop colorectal cancer during their lifetime, and as a result, some people have their colon removed as a preventative measure (Markman, 2022).

Some individuals inherit genetic syndromes from their parents that increase their risk of getting colorectal cancer. These syndromes come with mutations—in particular, genes that make it more likely that cancer will develop. Examples include Lynch syndrome, familial adenomatous polyposis and other rarer syndromes. Lynch syndrome is associated with about 2 percent to 4 percent of all cancers in the colon or rectum, according to the ACS. People with Lynch syndrome have a high risk of getting colorectal cancer at some point in their lifetime—up to 50 percent. Those who have Lynch syndrome and go on to develop colorectal cancer tend to get the cancer at an earlier than average age (Markman, 2022).

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. Unlike familial adenomatous polyposis (FAP), HNPCC syndrome usually involves only single colorectal adenomas or carcinomas that cannot be clinically distinguished from sporadic tumors. Clinical and familial criteria have therefore been defined to identify patients with HNPCC. Patients who meet the Amsterdam Criteria are HNPCC patients by definition. Currently the Amsterdam Criteria also still cover families with no evidence of a DNA repair defect in a tumor, in which the increased tumor risk is probably due to genetic causes that have not yet been identified (Steinke V, Engel C, Büttner R, et al., 2013)

HNPCC patients also include those who meet the weaker criteria of the Bethesda Guidelines and have a tumor with an MMR defect. The Bethesda Guidelines have a higher sensitivity but lower specificity than the Amsterdam Criteria regarding evidence of a mutation in an MMR gene. All patients carrying a cancer-causing germline mutation in an MMR gene (almost half of HNPCC patients) can also be said to have Lynch syndrome. However, in everyday clinical practice in Germany the terms “HNPCC” and “Lynch syndrome” are usually used synonymously (Steinke V, Engel C, Büttner R, et al., 2013).

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 differences among 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.

Approximately 20% of cases of colon cancer are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive CRC are at increased risk for CRC. Genetic susceptibility to CRC includes well-defined inherited syndromes, such as Lynch syndrome and FAP. Therefore, it is recommended that all patients with colon cancer be queried regarding their family history and considered for risk assessment (NCCN, 2023).

The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome. This testing is also relevant for adjuvant therapy planning for stage II disease and treatment selection in stage IV disease.

According to 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.

Amsterdam II Clinical Criteria
Three or more relatives with an associated cancer (colorectal, endometrium, small intestine, ureter or renal pelvis. All of the following criteria must be fulfilled:

- One should be a 1st degree relative of the other two; AND
- At least two or more successive generations are affected; AND
- One or more relatives with cancer associated with HNPCC should be diagnosed before the age of 50; AND
- Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma (if any); AND
- Tumors, if available, should be verified by pathologic examination; AND
- Modifications:

- Very small families, which cannot be further expanded, can be considered to have HNPCC with only two colorectal cancers in 1st 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; OR
- In families with two 1st degree relatives affected by colorectal cancer, the presence of a third relative with unusual early onset neoplasm or endometrial cancer is sufficient.

Revised Bethesda Guidelines

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

- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old; OR
- Presence of synchronous (at the same time) or metachronous (at another time, i.e., a recurrence of) colorectal carcinoma or other Lynch syndrome associated tumors, regardless of age; OR
- CRC with high microsatellite instability histology (MSI H) diagnosed in a patient less than 60 years old; OR
- CRC diagnosed in one or more 1st degree relatives with an HNPCC related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter, 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 an age younger than 50; OR
- CRC diagnosed in two or more 1st degree or 2nd degree relatives with HNPCC related tumor, regardless of age.

The NCCN Guidelines on Lynch Syndrome recommends that a universal screening strategy be the primary approach to identify CRC patients with LS. However, in other lower resources settings, other historic criteria for selecting patients for testing may be relevant. The Bethesda criteria are intended to help identify CRC patients whose tumors could be tested MMR defects, by MSI and/or IHC analysis, thereby identifying patients with a greater chance of having LS.

The NCCN panel recommends universal screening of all CRCs and endometrial cancers to maximize sensitivity for identifying individuals with LS and to simplify care processes. The panel also recommends considering tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, gastric, pancreas, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age at diagnosis. Counseling by an individual with expertise in genetics is not required prior to routine tumor testing. An infrastructure needs to be in place to handle screening results.

The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with a personal history of color or rectal cancer to identify individuals with Lynch Syndrome. This testing is also relevant for adjuvant chemotherapy planning for stage II disease and treatment selection in stage IV disease. NCCN also noted that to confirm the diagnosis of FAP or AFAP, a germline mutation in APC must be identified. A family history may be negative, since approximately30% of individuals have de novo APC germline mutations.

The National Cancer Institute noted most organizations have adopted a gene-specific approach to these recommendations. All of the screening recommendations assume findings are normal. A more aggressive screening schedule might be considered on an individualized basis.

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 (eg, 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 (eg, 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)

81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
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
0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamarroma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2. MLH1, MSH, MSH6, MUTYH, PMS2, PTEN and TP53) (List separately in addition to code for primary procedure)

**See related Highmark Wholecare medical policy "MP-062-MD-PA BRAF Mutation Analysis"*

Diagnosis Codes

ICD-10 Code	Description
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
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
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon

C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.3	Malignant neoplasm of bilateral ovaries
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C60.1	Malignant neoplasm of glans penis
C65.1	Malignant neoplasm of right renal pelvis

C65.2	Malignant neoplasm of left renal pelvis
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
D01.49	Carcinoma in situ of other parts of intestine
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
D23.21	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
D23.39	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
D23.61	Other benign neoplasm of skin of right upper limb, including shoulder
D23.62	Other benign neoplasm of skin of left upper limb, including shoulder
D23.71	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, unspecified
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
D49.0	Neoplasm of unspecified behavior of digestive system
K63.5	Polyp of colon

L85.8	Other specified epidermal thickening
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

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

Reference Sources

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. February 18, 2004. Accessed on May 6, 2016.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Uterine Neoplasms, v 2.2024. Accessed on July 30, 2024.

National Comprehensive Cancer Network (NCCN). Genetic/Familial High-Risk Assessment: Colorectal. Version 2.2023. October 30, 2023. Accessed on July 30, 2024.

Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. Managed Care Operations Memorandum. Accessed on July 20, 2022.

National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Colorectal screening. Version 1.2023. May 17, 2023. Accessed on July 31, 2023.

Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. April 3, 2014. Accessed on May 24, 2016.

Lin JS, Webber EM, Beil TL, Goddard KA, Whitlock EP. Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults [Internet]. Agency for Healthcare Research and Quality (AHRQ). February 2012. Accessed on May 24, 2016.

National Library of Medicine (NLM). Genetics Home Reference. EPCAM. Updated June 26, 2023. Accessed on July 31, 2023.

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. December 3, 1997. Accessed on May 24, 2016.

National Cancer Institute. Genetics of Colorectal Cancer (PDQ)-Health Professional Version. Last updated December 17, 2020. Accessed on July 8, 2021.

Deibert B, Ferris L, Sanchez N, Weishaar P. The link between colon cancer and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Am J Ophthalmol Case Rep. September 15, 2019. Accessed on July 27, 2020.

Markman M. Cancer Treatment Centers of America. Colorectal cancer types. March 16, 2022. Accessed on July 21, 2022.

Steinke V, Engel C, Büttner R, et al. Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome. Dtsch Arztebl Int. January 2013. Accessed on July 21, 2022.