



PARAMOUNT

# Genetic Testing for Lynch Syndrome and Polyposis Syndromes

Policy Number: PG0302

Last Review: 06/26/2019

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ADVANTAGE | ELITE | HMO  
INDIVIDUAL MARKETPLACE |  
PROMEDICA MEDICARE  
PLAN | PPO

## GUIDELINES

**This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.**

## SCOPE

Professional

Facility

## DESCRIPTION

**Lynch syndrome**, often called hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited disorder that increases the risk of many types of cancer, particularly cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the stomach, small intestine, pancreas, hepatobiliary tract, ureter, renal pelvis, and brain. Women with this disorder have a high risk of cancer of the ovaries and lining of the uterus (the endometrium). Additionally, individuals with Lynch syndrome have an increased risk for sebaceous adenomas, sebaceous carcinoma, and keratocanthomas.

Pathogenic variants, also called mutations, in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* are associated with Lynch syndrome. The *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes are involved in the repair of mistakes that occur when DNA is copied in preparation for cell division (a process called DNA replication). Mutations in any of these genes prevent the proper repair of DNA replication mistakes. As the abnormal cells continue to divide, accumulated mistakes can lead to uncontrolled cell growth and possibly cancer. Mutations in the *EPCAM* gene also lead to impaired DNA repair, although the gene is not itself involved in this process. The *EPCAM* gene lies next to the *MSH2* gene on chromosome 2; certain *EPCAM* gene mutations cause the *MSH2* gene to be turned off (inactivated), interrupting DNA repair and leading to accumulated DNA mistakes. Although mutations in the Lynch syndrome genes predispose individuals to cancer, not all people who carry these mutations develop cancerous tumors.

**Familial adenomatous polyposis (FAP)** is an inherited disorder characterized by many adenomatous polyps (growths) in the colon as early as their teenage years. Unless the colon is removed, these type of polyps will become malignant (cancerous). The average age at which an individual develops colon cancer in classic familial adenomatous polyposis is 39 years. Some people have a variant of the disorder, called attenuated familial adenomatous polyposis, in which individuals have less polyps than classic FAP and polyp growth is delayed. The average age of colorectal cancer onset for attenuated familial adenomatous polyposis is 55 years.

Mutations in the *APC* gene cause both classic and attenuated familial adenomatous polyposis. The number of adenomatous polyps and time in which malignant transformation occurs varies depending on the location of the *APC* mutation. *APC* works as a tumor suppressor meaning that it is supposed to control cell growth and division. When an *APC* mutation is present, cell overgrowth occurs (i.e. colon polyps).

Biallelic (two) mutations in the *MUTYH* gene cause autosomal recessive ***MUTYH*-Associated Polyposis or MAP** (also called MYH-associated polyposis). Mutations in this gene prevent cells from correcting mistakes that are made when DNA is copied (DNA replication) in preparation for cell division. As these mistakes build up in a person's DNA, the likelihood of cell overgrowth increases, leading to colon polyps and the possibility of colon cancer.

## **POLICY**

**Genetic testing for Lynch syndrome, FAP/AFAP, and MAP requires prior authorization for all product lines.**

**Lynch syndrome, FAP/AFAP, and MAP genetic testing related to family history information solely is non-covered for Elite/ProMedica Medicare Plan.**

**Multigene panels (including next-generation sequencing [NGS]) for hereditary cancer susceptibility require prior authorization (see medical policy PG0453).**

**Pre-test and post-test genetic counseling is recommended when hereditary cancer genetic testing is being offered (ACOG, ASCO, NCCN, NSGC). Documentation of pre-test genetic counseling is required for coverage of Lynch syndrome and Polyposis syndrome genetic testing.**

**Informed consent is a necessary component of pre-test counseling and should include discussion of the following topics (NSGC, 2012):**

- **Purpose of test and who to test (i.e. discussion of limitations to testing an unaffected individual in the absence of a known familial mutation)**
- **General information about gene(s) included in the testing**
- **Possible test results (positive, negative, uncertain findings)**
- **Technical aspects and accuracy of test**
- **Economic considerations**
- **Potential for genetic discrimination (i.e. discussion of the Genetic Information Non-Discrimination Act, and applicable state laws)**
- **Psychosocial aspects**
- **Confidentiality**
- **Utilization of test results (i.e. potential medical management options)**
- **Alternatives to testing**

**A 3-generation pedigree should be completed during pre-test counseling. The 3-generation pedigree is required for prior authorization of Lynch syndrome, FAP/AFAP, and MAP genetic testing.**

**In circumstances where the individual is unaffected by cancer but Lynch syndrome genetic testing is being considered due to family history (in the absence of a known familial mutation), further information will be required to determine medical necessity<sup>1</sup>.**

Genetic testing for Lynch syndrome, FAP/AFAP, and MAP may be covered with prior authorization. Paramount's criteria for these tests are closely aligned with National Comprehensive Cancer Network<sup>®</sup> (Version 1.2018) criteria to determine medical necessity.

Close relatives are defined as:

- first-degree (parents/full, siblings/children),
- second-degree (grandparents/aunts/uncles/nephews/nieces/grandchildren/half-siblings) and
- third-degree (great-grandparents/great-aunts/great-uncles/great-grandchildren/first cousins/half-uncles/half-aunts) relatives on the same side of the family.

### **HMO, PPO, Individual Marketplace, Elite/ProMedica Medicare Plan, Advantage**

Genetic testing for Lynch is considered medically necessary when ANY of the following criteria are met:

- An individual with colorectal or endometrial cancer and any of the following:
  - Diagnosed <50 years of age
  - Another synchronous or metachronous Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain, biliary tract, small intestinal cancers, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas)
  - ≥1 first-degree or second-degree relative with Lynch syndrome-related cancer diagnosed <50 years of age
  - ≥2 first-degree or second-degree relatives with Lynch syndrome-related cancer regardless of age
  - An individual with colorectal or endometrial cancer at any age with tumor showing evidence of mismatch repair (MMR) deficiency through microsatellite instability (MSI) or loss of MMR protein expression on immunohistochemistry (IHC)
- An individual with a Lynch syndrome-related cancer with a ≥5% risk of having a MMR gene mutation based upon predictive models (PREMM5, MMRpro, MMRpredict)
- An individual with a colorectal tumor with MSI-high (MSI-H) histology (i.e. presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) diagnosed ≤60 years of age
- Individuals who are affected by a Lynch syndrome related cancer and who have a close relative with a known Lynch syndrome mutation.

### **HMO, PPO, Individual Marketplace, Advantage (Family history indication)**

Lynch syndrome genetic testing is considered medically necessary based upon family history information in the absence of an affected relative<sup>1</sup> being available for testing with ANY of the following criteria:

- ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 years or age
- ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-related cancer
- ≥2 first-degree or second-degree relatives with Lynch syndrome-related cancer, including ≥1 diagnosed <50 years of age
- ≥3 first-degree or second-degree relatives with Lynch syndrome-related cancers, regardless of age
- An individual with a ≥5% risk of having an MMR gene mutation based upon predictive models (PREMM5, MMRpro, MMRpredict)
- For individuals who have a first-degree or second-degree relative with a known Lynch syndrome mutation, genetic testing is medically necessary.

### **HMO, PPO, Individual Marketplace, Elite/ProMedica Medicare Plan, Advantage**

Genetic testing for Familial Adenomatous Polyposis (FAP)/Attenuated Familial Adenomatous Polyposis (AFAP) is considered medically necessary when ANY of the following criteria are met:

- Personal history of ≥10 cumulative adenomatous colon polyps
- Known *APC* mutation in a first or second-degree relative (excluding Elite/ProMedica Medicare Plan members)
- Personal history of desmoid tumor
- Personal history of hepatoblastoma
- Personal history of cribriform-morular variant of papillary thyroid cancer
- Personal history of multifocal/bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE)

### **COVERAGE CRITERIA**

#### **HMO, PPO, Individual Marketplace, Elite/ProMedica Medicare Plan, Advantage**

Genetic testing for *MUTYH*-Associated Polyposis (MAP) is considered medically necessary when ANY of the following criteria are met:

- Personal history of ≥10 cumulative adenomatous polyps

- Known *MUTYH* mutation(s) in the family (excluding Elite/ProMedica Medicare Plan members)
- Individual meets criteria #1 or #3 for serrated polyposis syndrome (see below) and has a personal history of at least some adenomatous polyps

Serrated Polyposis Syndrome definition (clinical diagnosis is considered when an individual meets one of the following):

- 1) At least 5 serrated polyps proximal to the sigmoid colon with 2 or more of these being >10mm
- 2) Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
- 3) ≥20 serrated polyps of any size, but distributed throughout the colon

\*Please note that serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas.

## CODING/BILLING INFORMATION

The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

CPT CODES	
81201	<i>APC</i> (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	<i>APC</i> (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	<i>APC</i> (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81210	<i>BRAF</i> (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81288	<i>MLH1</i> ( <i>mutL</i> homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	<i>MLH1</i> ( <i>mutL</i> homolog, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	<i>MLH1</i> ( <i>mutL</i> homolog, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	<i>MLH1</i> ( <i>mutL</i> homolog, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	<i>MSH2</i> ( <i>mutS</i> homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	<i>MSH2</i> ( <i>mutS</i> homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome); known familial variants
81297	<i>MSH2</i> ( <i>mutS</i> homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome); duplication/deletion variants
81298	<i>MSH6</i> [ <i>mutS</i> homolog 6 ( <i>E.coli</i> )] (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	<i>MSH6</i> [ <i>mutS</i> homolog 6 ( <i>E.coli</i> )] (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	<i>MSH6</i> [ <i>mutS</i> homolog 6 ( <i>E.coli</i> )] (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 of deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81317	<i>PMS2</i> [ <i>postmeiotic segregation increased 2</i> ( <i>S. cerevisiae</i> )] (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

<b>81318</b>	<i>PMS2</i> [postmeiotic segregation increased 2( <i>S. cerevisiae</i> )] (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
<b>81319</b>	<i>PMS2</i> [postmeiotic segregation increased 2( <i>S. cerevisiae</i> )] (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
<b>81403</b>	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): <ul style="list-style-type: none"> <li>• <i>EPCAM</i> (<i>epithelial cell adhesion molecule</i>) (eg, Lynch syndrome), duplication/deletion analysis</li> </ul>
<b>81401</b>	Molecular pathology procedure, Level 2 (eg, 2-10SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) <ul style="list-style-type: none"> <li>• <i>MUTYH</i> (<i>mutY homolog [E. coli]</i>) (eg, MYH-associated polyposis), common variants (eg, Y165C,G382D)</li> </ul>
<b>81406</b>	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, cytogenomic array analysis for neoplasia) <ul style="list-style-type: none"> <li>• <i>MUTYH</i> full gene sequence</li> </ul>
<b>81435</b>	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous 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
<b>81436</b>	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis);duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

## REVISION HISTORY EXPLANATION

### **ORIGINAL EFFECTIVE DATE: 09/09/2014**

**09/09/14:** Policy created to reflect most current clinical evidence per Medical Policy Steering Committee.

**04/22/16:** Added codes 81210 and 81288. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

**10/27/17:** Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

**06/26/19:** Policy reviewed and updated to reflect most current clinical evidence per the National Comprehensive Cancer Network®. Components of genetic counseling were added. Additionally a 3-generation pedigree is now required as well as an additional form for individuals who are unaffected but are pursuing genetic testing due to family history and have no known mutation in the family.

**07/09/19:** Title was changed to Genetic Testing for Lynch syndrome and Polyposis syndromes. Information in the description section was made more specific. No significant content changes were made. Information pertaining to brand names was deleted. Information regarding informed consent/pre-test counseling was added. Additionally, added requirement for 3-generation pedigree as well as a form for individuals who are unaffected and are pursuing genetic testing based upon family history (no known mutation in the family). Added requirement for documentation of pre-test genetic counseling for coverage. Testing criteria were updated to what is currently recommended by NCCN. Some of the significant changes include: deletion of criteria related to colorectal adenomas applying to Lynch criteria, deletion of the specific criteria for EPCAM coverage, adding criteria for ≥5% risk from predictive model for Lynch, and adding criteria related to having a known mutation in the family. Additionally, added having 3 or more first and second degree relatives with Lynch syndrome related cancers as a criteria. Added information about serrated polyposis syndrome related to MAP. Added relevant CPT codes. Added statement regarding multi-gene panel policy. Also added several references. Limited coverage for testing for Elite line- require individual to be personally affected by cancer or polyposis for coverage.

**07/25/19:** Corrected medical policy reference from PG0451 to PG0453. Deleted the comment "tracked changes".

**12/19/2020:** Medical policy placed on the new Paramount Medical Policy Format



## REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services  
Ohio Department of Medicaid  
American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services  
Industry Standard Review  
Hayes, Inc.  
National Comprehensive Cancer Network® (NCCN), Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2018  
The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin, Lynch Syndrome, Number 147, November 2014  
American Society of Clinical Oncology (ASCO) Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility, Volume 33, Number 31, November 1, 2015  
National Society of Genetic Counselors (NSGC) Practice Guideline: Risk Assessment and Genetic Counseling for Hereditary Breast and Ovarian Cancer, Volume 21, April 2012 (Components of Informed Consent)  
Identification of Individuals at Risk for Lynch Syndrome Using Targeted Evaluations and Genetic Testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer Joint Practice Guideline  
American Gastroenterological Association Medical Position Statement: Hereditary Colorectal Cancer and Genetic Testing, Volume 121, July 2001  
Genetics Home Reference, National Institute of Health, U.S. National Library of Medicine, *APC* gene  
Genetics Home Reference, National Institute of Health, U.S. National Library of Medicine, *MUTYH* gene  
Genetics Home Reference, National Institute of Health, U.S. National Library of Medicine, Lynch syndrome