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.

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, liver, gallbladder ducts, upper urinary tract, brain, and skin. Additionally, women with this disorder have a high risk of cancer of the ovaries and lining of the uterus (the endometrium). People with Lynch syndrome may occasionally have noncancerous (benign) growths (polyps) in the colon, called colon polyps. In individuals with this disorder, colon polyps occur earlier but not in greater numbers than they do in the general population.

Variations in the MLH1, MSH2, MSH6, PMS2, or EPCAM gene increase the risk of developing 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, the 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 these 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 cancer of the large intestine (colon) and rectum. People with the classic type of familial adenomatous polyposis may begin to develop multiple noncancerous (benign) growths (polyps) in the colon as early as their teenage years. Unless the colon is removed, these 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 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. These mutations affect the ability of the cell to maintain normal growth and function. Cell overgrowth resulting from mutations in the APC gene leads to the colon polyps seen in familial adenomatous polyposis. Although most people with mutations in the APC gene will develop colorectal cancer, the number of polyps and the time frame in which they become malignant depend on the location of the mutation in the gene.

Mutations in the MUTYH gene cause autosomal recessive familial adenomatous polyposis (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 requires prior authorization for all product lines.

HMO, PPO, Individual Marketplace, Elite, Advantage
Genetic testing for Lynch syndrome to detect mutations in the HNPCC genes, associated with genetic counseling, is considered medically necessary when ANY of the following criteria are met:
  • The individual has 2 or more HNPCC-related tumors, (colorectal, endometrial, biliary tract, pancreas, ureter or renal pelvis, ovarian, brain, gastric, or small intestinal cancers, sebaceous gland adenomas or keratoacanthomas), including synchronous and metachronous tumors; or
  • The individual has a history of colorectal cancer and a first-degree relative with colorectal cancer diagnosed prior to age 50; or
• The individual has a history of colorectal cancer and a first-degree relative with an HNPCC-related cancer diagnosed prior to age 50; or
• The individual has a history of colorectal cancer and a first-degree relative with colorectal adenoma diagnosed prior to age 40; or
• The individual has colorectal cancer or endometrial cancer diagnosed prior to age 50; or
• The individual has a colorectal adenoma diagnosed prior to age 40; or
• The individual has a first- or second-degree relative with a known HNPCC mutation (Lynch syndrome in family); or
• The individual has personal history of colorectal or endometrial cancer and tumor shows high microsatellite instability (MSI).

For individuals with a family history of potentially HNPCC related cancer, genetic testing to detect mutations in the HNPCC genes, associated with genetic counseling, is considered medically necessary when they have a relative who would meet ANY of the following criteria, but that relative is not available for testing:
• The individual for whom the test is requested, has a first- or second-degree relative with 2 or more HNPCC-related tumors (colorectal, endometrial, biliary tract, pancreas, ureter or renal pelvis, ovarian, brain, gastric, or small intestinal cancers, or sebaceous gland adenomas or keratoacanthomas), including synchronous and metachronous tumors; or
• The individual for whom the test is requested, has a first- or second-degree relative with a history of colorectal cancer and that relative has a first-degree relative with colorectal cancer diagnosed prior to age 50; or
• The individual for whom the test is requested, has a first- or second-degree relative with a history of colorectal cancer and that relative has a first-degree relative with an HNPCC-related cancer diagnosed prior to age 50; or
• The individual for whom the test is requested, has a first- or second-degree relative with colorectal adenoma diagnosed prior to age 40.

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 BOTH criteria are met:
1. The tumor is negative for MSH2 and MSH6 expression as demonstrated by IHC; and
2. The individual tested negative for a MSH2 germline mutation.

APC and MYH gene testing for Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP), or MYH associated polyposis (MAP) is covered for the following individuals who are diagnosed with or personal history of at least one of the following:
• A beneficiary with ≥ 10 cumulative colorectal adenomas over a lifetime
• Testing for APC gene mutations should precede testing for the less common MYH mutation
• Cribriform morular variant of papillary thyroid cancer
• Hepatoblastoma
• Desmoid tumor
• Ten or fewer colorectal adenomatous polyps and at least one of the following:
  1. First or second-degree relative with FAP or AFAP
  2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
  3. Dental abnormalities (unerupted teeth, congenital absence of teeth, extra teeth, dentigerous cysts, and odontomas)
  4. Osteomas
  5. Epidermoid cysts
  6. Fibromas
  7. Pancreatic adenocarcinomas
  8. Medulloblastoma
  9. Small bowel polyps or carcinoma

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
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
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<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
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<td>81210</td>
<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
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<td>81292</td>
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<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81296</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td>81297</td>
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<td>MSH6 (mutS homolog 6 (E.coli)) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81300</td>
<td>MSH6 (mutS homolog 6 (E.coli)) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td>81301</td>
<td>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</td>
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<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2(S. cerevisiae)) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2(S. cerevisiae)) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2(S. cerevisiae)) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons):</td>
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<tr>
<td></td>
<td>• EPCAM (epithelial cell adhesion molecule) (eg, Lynch syndrome), duplication/deletion analysis</td>
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**REVISION HISTORY EXPLANATION**
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 Medical Policy Steering Committee.

**REFERENCES/RESOURCES**
Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services
Ohio Department of Medicaid [http://ifs.ohio.gov/](http://ifs.ohio.gov/)
Industry Standard Review Hayes, Inc.