### Genetic Testing, Colorectal Cancer

Including Micro-Satellite Instability (MSI), Lynch Syndrome/Hereditary Non-Polyposis Colorectal Cancer (MLH1, MSH2, MSH6, PMS2, EPCAM), Familial Adenomatous Polyposis Coli and Attenuated Familial Adenomatous Polyposis Coli (APC Genetic Testing), MUTYH-Associated Polyposis (MAP)/MYH Associated Polyposis

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<th>CPT/HCPCS CODES</th>
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<td>81201, 81202, 81203, 81288, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81317, 81318, 81319, 81401, 81403, 81406, 81435, 81436</td>
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### CRITERIA

**LYNCH SYNDROME (LS)/HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC), MUST MEET ALL OF THE FOLLOWING:**

1. The results of the genetic testing will directly impact surveillance or treatment of the member.

2. One of the following criteria is met:
   a. Amsterdam II Criteria (must meet 1-5):
      1) An LS/HNPCC-associated cancer (colorectal, endometrium, small bowel, ureter, renal pelvis) is present in at least three related members in the family; **and**
      2) One family member must be a first-degree relative\(^1\) of the other two; **and**
      3) The LS/HNPCC-associated cancers are present in 2 successive generations of the family; **and**
      4) At least one family member has been diagnosed with cancer associated with LS/HNPCC < 50 years of age; **and**
      5) Familial adenomatous polyposis (FAP see below) has been ruled out.
   b. Revised Bethesda Criteria, for testing colorectal tumors for microsatellite instability (MSI) (Must meet one of the following):
      1) Colorectal cancer diagnosed in an member < 50 years of age;
      2) Presence of synchronous or metachronous LS/HNPCC-associated tumors, regardless of age;
      3) Colorectal cancer with the microsatellite instability-high histology\(^2\) diagnosed in an member < 60 years of age;
      4) Colorectal cancer diagnosed in an member with one or more first-degree relative(s) with an LS/HNPCC-related cancer and with one of the cancers being diagnosed < 50 years of age;
      5) Colorectal cancer diagnosed in an member with two or more first- or second-degree relatives with LS/HNPCC-related cancers, regardless of age.\(^1\)
   c. The member has endometrial cancer diagnosed <50 years of age.
   d. Lynch Syndrome has been definitively diagnosed in a first- or second-degree relative.
   e. The PREMM \(^{[1,2,6]}\) mutation prediction model yields a result of ≥ 5%.

   [http://premm.dfci.harvard.edu/](http://premm.dfci.harvard.edu/)

\(^1\) First-degree relatives include parents, siblings or children; Second-degree relatives include grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings.

\(^2\) Instability-high histology includes the presence of tumor infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.
**MEDICAL PRE-AUTHORIZATION CRITERIA**

**CRITERIA (continued)**

FAMILIAL ADENOMATOUS POLYPOSIS COLI (FAP) OR ATTENUATED FAP MUST MEET ALL OF THE FOLLOWING:

1. The results of the genetic testing will directly impact surveillance or treatment of the member.
2. One of the following criteria is met:
   a. The member has more than 10 colorectal adenomatous polyps;
   b. The member has a first-degree relative(s) with a known APC mutation;
   c. The member has a personal history of a desmoid tumor.

**NOTE:** APC negative members should be tested for MUTYH. Members with Serrated Polyposis Syndrome with associated adenomas should also be tested for MUTYH.

**DEFINITIONS**

**Lynch Syndrome (LS)/Hereditary Nonpolyposis Colorectal Cancer (HNPCC):** Accounts for 3-5% of all colorectal cancer. LS/HNPCC is an autosomal dominant condition caused by one of several DNA mismatch repair genes (MSH2 and MLH1 predominantly; MSH6 to a lesser extent). Unlike FAP, members with LS/HNPCC do not have an unusual number of colonic polyps. In addition to colorectal cancer (predominantly right-sided), members with LS/HNPCC have an increased risk of extracolonic cancers, most commonly endometrial. Other associated cancers include ovarian, stomach, small bowel, pancreatic, hepatobiliary, brain (usually glioblastoma as seen in Turcot Syndrome), ureteral and renal pelvis. In addition, sebaceous gland adenomas and keratocantomas are seen in Muir-Torre Syndrome (a rare subtype of LS/HNPCC).

Although the Amsterdam and Bethesda criteria are sometimes used interchangeably, they were created to serve different purposes. The Amsterdam criteria are used to identify members who meet the definition of LS/HNPCC. The Bethesda criteria are intended to help identify tumors that should be tested for microsatellite instability, thereby identifying members at risk for LS/HNPCC. If microsatellite instability is high, then more specific gene testing is appropriate (MLH1, MSH2, MSH6, PMS2).

**Familial Adenomatous Polyposis (FAP)—Also called Gardner Syndrome, Familial Polyposis Coli or Adenomatous Polyposis Coli (APC).** FAP is an autosomal dominant condition caused by mutations of the APC gene. Members with FAP have multiple (>100) adenomatous polyps in the colon and rectum developing after the first decade of life. Members with FAP may also have polyps in the upper GI, dental abnormalities (especially supernumerary teeth and/or ondontomas) and extraintestinal manifestations such as osteomas and epidermoid cysts and fibromas, desmoid tumors, congenital hypertrophy of retinal pigment epithelium (CHRPE) and other malignant changes such as papillary thyroid cancer, gastric and pancreatic cancers, hepatoblastoma and medulloblastoma.

**Attenuated FAP—**A heterogenous clinical entity. Members have fewer than 100 adenomatous polyps in the colorectum. The incidence is unknown but may be similar to FAP. Testing of the APC gene also plays a role in the evaluation of members with suspected attenuated FAP.

**MUTYH-Associated Polyposis (MAP)/MYH-Associated Polyposis—**Members have multiple colorectal adenomas with or without cancer. MAP is an autosomal recessive condition resulting from defects in the Mut Y homolog (MUTYH) genes. This condition may account for a portion of members who present with multiple adenomas like FAP but are negative for APC gene mutations. Members meeting criteria for FAP or Attenuated FAP and who do not have an identifiable APC gene mutation are appropriate for MYH genetic testing.

**Serrated Polyposis Syndrome (SPS)—Also known as Hyperplastic Polyposis Syndrome.** SPS is an uncommon condition resulting in multiple colorectal hyperplastic polyps and sessile serrated adenomas/polyps or adenomas.

To view ConnectiCare's list of policies on various medical treatments and emerging technologies, go to [www.connecticure.com/provider/MedicalPolicyCriteria.aspx](http://www.connecticure.com/provider/MedicalPolicyCriteria.aspx)
NOTE: There are multiple laboratories in the U.S. that perform colorectal cancer screening. At the present, there is no mechanism to determine whether any of these laboratories should be used preferentially. Myriad Genetic Laboratories is one of these laboratories; Colaris is the name of their proprietary genetic testing panel for LS/HNPCC and Colaris-AP is the name of their genetic testing panel for FAP/AFAP.

REFERENCES


