Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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Section: Medicine
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I. Description

There are currently 2 well-defined types of hereditary colorectal cancer, familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer or HNPCC). Lynch syndrome has been implicated in some endometrial cancers as well.

Familial adenomatous polyposis and associated variants

FAP typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will go on to develop colorectal cancer. The mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP accounts for about 1% of colorectal cancer and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina referred to as congenital hypertrophy of the retinal pigment epithelium (CHRPE). FAP associated with these collective extraintestinal manifestations is sometimes referred to as Gardner syndrome. FAP may also be associated with central nervous system (CNS) tumors, referred to as Turcot syndrome.

Germline mutations in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Mutations in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. A specific APC gene mutation (I1307K) has been found in subjects of Ashkenazi Jewish descent, which may explain a portion of the familial colorectal cancer occurring in this population.

A subset of FAP patients may have attenuated FAP (AFAP), typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, colorectal cancer occurring at an average age of 50-55 years, but a high lifetime risk of colorectal cancer of about 70% by age 80 years. The risk of extra-intestinal cancer is lower compared to classical FAP but still high at an estimated cumulative lifetime risk of 38% compared to the general population. Only 30% or fewer of AFAP patients have APC mutations; some of these patients instead have mutations in the MUTYH (formerly MYH) gene and are then diagnosed with MUTYH-associated polyposis (MAP). MAP occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH mutations are associated with a cumulative colorectal cancer risk of about 80% by age 70, whereas monoallelic MUTYH mutation-associated risk of colorectal cancer
appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk colorectal cancer predisposition is autosomal recessive in contrast to FAP. When relatively few (ie, between 10 and 99) adenomas are present and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include APC, MUTYH if APC is negative for mutations, and screening for mutations associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome.

Genetic testing for APC mutations may be considered for the following types of patients:

- Family members of patients with FAP and a known APC mutation. Those without the specific mutation have not inherited the susceptibility gene and can forego intense surveillance (although they retain the same risk as the general population and should continue an appropriate level of surveillance).
- Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome. These patients do not meet the clinical diagnostic criteria for classical FAP and have few adenomatous colonic polyps.
- Patients with colon cancer with a clinical picture or family history consistent with classical FAP.

**Lynch syndrome**

Patients with Lynch syndrome have a predisposition to colorectal cancer and other malignancies as a result of an inherited mutation in a DNA mismatch repair (MMR) gene. Lynch syndrome includes those with an existing cancer and those who have not yet developed cancer. The term “HNPCC” originated prior to the discovery of explanatory MMR mutations for many of these patients and now includes some who are negative for MMR mutations and likely have mutations in as-yet unidentified genes. For purposes of clarity and analysis, the use of Lynch syndrome in place of HNPCC has been recommended in several recent editorials and publications.

Lynch syndrome is estimated to account for 3% to 5% of all colorectal cancer and is also associated with an increased risk of other cancers such as endometrial, ovarian, urinary tract, and biliary tract cancer. Lynch syndrome is associated with a risk of developing colorectal cancer by age 70 years of approximately 27% to 45% for men, and 22% to 38% for women, after correction for ascertainment bias. Lynch syndrome patients who have colorectal cancer also have an estimated 16% risk of a second primary within 10 years.

Lynch syndrome is associated with any of a large number of possible mutations in 1 of several MMR genes, known as MLH1, MSH2, MSH6, PMS2 and rarely MLH3. Risk of all Lynch syndrome-related cancers is markedly lower for carriers of a mutation in the MSH6 and PMS2 genes, although for most cancers still significantly higher than that of the general population. Estimated cumulative risks of any associated cancer for a carrier of a mutation in any MMR gene do not begin to increase until after age 30 years.

Lynch syndrome mutations are heterozygous; that is, only one of the 2 gene alleles contains a mutation. In rare cases both alleles contain the mutation, ie, biallelic MMR gene mutations. This unusual syndrome has been described in multiple families and is to a large extent the result of consanguinity. Children with biallelic MMR mutations may develop extra-colonic cancers in childhood, such as brain tumors, leukemias, or lymphomas. Those unaffected or surviving early malignancies are at high risk of
Genetic Testing for Lynch Syndrome/Colorectal Cancer and Polyposis Syndromes

later colorectal cancer (average age of colorectal cancer diagnosis 16.4 years). Family history may not suggest Lynch syndrome. Prior to cancer diagnosis, patients may have multiple adenomatous polyps and thus may have an initial differential diagnosis of attenuated FAP versus MUTYH-associated polyposis versus Lynch syndrome.

About 70% of Lynch syndrome patients have mutations in either MLH1 or MSH2. Testing for MMR gene mutations is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2 testing. Large gene sizes and the difficulty of detecting mutations in these genes make direct sequencing a time- and cost-consuming process. Thus, additional indirect screening methods are needed to determine which patients should proceed to direct sequencing for MMR gene mutations. Available screening methods are microsatellite instability (MSI) testing or immunohistochemical (IHC) testing. BRAF testing is an optional screening method that may be used in conjunction with IHC testing for MLH1 to improve efficiency. A methylation analysis of the MLH1 gene can largely substitute for BRAF testing, or be used in combination to slightly improve efficiency.

Mutations in MMR genes result in a failure of the mismatch repair system to repair errors that occur during the replication of DNA in tumor tissue. Such errors are characterized by the accumulation of alterations in the length of simple, repetitive microsatellite (2 to 5 base repeats) sequences that are distributed throughout the genome, termed microsatellite instability (MSI) and resulting in an MSI-high tumor phenotype. MSI testing was standardized subsequent to a 2004 National Cancer Institute (NCI) workshop.(6) Methodologic studies have also shown the importance of laser microdissection of the tumor tissue, comparison of tumor and normal cells, and a minimum proportion of tumor in relation to the quality of the test results. While the sensitivity of MSI testing is high, the specificity is low because approximately 10% of sporadic colorectal carcinoma (CRC) is MSI-positive due to somatic hypermethylation of the MLH1 promoter. Additionally, some tumors positive for MSH6 mutations are associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR mutation testing.

Absent or reduced protein expression may be a consequence of an MMR gene mutation. IHC assays for the expression of MLH1, MSH2, MSH6, and PMS2 can be used to detect loss of expression of these genes and to focus sequencing efforts on a single gene. It is also possible for IHC assays to show loss of expression, and thus indicate the presence of a mutation, when sequencing is negative for a mutation. In such cases, mutations may be in unknown regulatory elements and cannot be detected by sequencing of the protein coding regions. Thus IHC may add additional information.

The BRAF gene is often mutated in colorectal cancer; when a particular BRAF mutation (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present; to date no MLH1 gene mutations have been reported. Therefore, patients negative for MLH1 protein expression by IHC, and therefore potentially positive for an MLH1 mutation, could first be screened for a BRAF mutation. BRAF-positive samples need not be further tested by MLH1 sequencing. MLH1 gene methylation largely correlates with the presence of BRAF-V600E and in combination with BRAF testing can accurately separate Lynch from sporadic colorectal cancer in IHCMLH1-negative cases.

Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR mutations, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria (low sensitivity but high specificity) and the Bethesda guidelines (better sensitivity but poorer specificity). While family history is an important risk factor and should not be discounted in counseling families, it has poor sensitivity and specificity for identifying Lynch syndrome. Based on this and other evidence, the Evaluation of Genomic Applications in Practice and Prevention
(EGAPP) Working Group recommended testing all newly diagnosed patients with colorectal cancer for Lynch syndrome, using a screening strategy based on MSI or IHC (+ BRAF) followed by sequencing in screen-positive patients. This recommendation includes genetic testing for the following types of patients:

- Family members of Lynch syndrome patients with a known MMR mutation; family members would be tested only for the family mutation; those testing positive would benefit from early and increased surveillance to prevent future colorectal cancer.
- Patients with a differential diagnosis of Lynch syndrome vs. attenuated FAP vs. MYH-associated polyposis [MAP].
- Lynch syndrome patients. Genetic testing of the proband with colorectal cancer likely benefits the proband where Lynch syndrome is identified and appropriate surveillance for associated malignancies can be initiated and maintained and benefits family members by identifying the family mutation.

Recently, novel deletions have been reported to affect the expression of the MSH2 MMR gene in the absence of a MSH2 gene mutation, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule, are responsible. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and/or IHC shows a lack of MSH2 expression, but no MSH2 mutation is found by sequencing.

Separately from patients with EPCAM deletions, rare Lynch syndrome patients have been reported without detectable germline MMR mutations although IHC testing demonstrates a loss of expression of one of the MMR proteins. In at least some of these cases, research has identified germline "epimutations," ie, methylation of promoter regions that control the expression of the MMR genes. Such methylation may be isolated or in conjunction with a linked genetic alteration near the affected MMR gene. The germline epimutations may arise de novo or may be heritable in either Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic colorectal cancer wherein the tumor tissue may show MLH1 promoter methylation and IHC nonexpression, but the same is not true of germline cells. Clinical testing for Lynch syndrome-related germline epimutations is not routine but may be helpful in exceptional cases. Epimutations as a cause of Lynch syndrome are described only for informational purposes; no policy statement is made regarding this testing.

Female patients with Lynch syndrome have a predisposition to endometrial cancer. Lynch syndrome is estimated to account for 2% of all endometrial cancers in women and 10% of endometrial cancers in women younger than 50 years of age. Female carriers of the germline mutations MLH1, MSH2, MSH6, and PMS2 have an estimated 40-62% lifetime risk of developing endometrial cancer, as well as a 4 to 12% lifetime risk of ovarian cancer.

For this policy, family member and at-risk relatives refer to first-degree and in some cases, second-degree relatives. All references to polyps in this policy are considered to be adenomatous polyps.

II. Criteria/Guidelines

A. Genetic testing is covered only when the testing will impact the clinical management of the patient in terms of improving health outcomes.

B. Genetic testing for APC gene mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the following patients:
1. At-risk relatives (first- or second-degree) of patients with FAP and/or a known APC mutation.
2. Patients with a differential diagnosis of attenuated FAP vs. MYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations, MYH mutations, or screening for MMR mutations depends upon clinical presentation.

C. Genetic testing for MYH gene mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the following patients:
1. Patients with a differential diagnosis of attenuated FAP versus MYH-associated polyposis versus Lynch syndrome and a negative test result for APC gene mutations. Family history of no parents or children with FAP is consistent with MYH-associated polyposis (autosomal recessive).

D. Genetic testing for mismatch repair (MMR) gene mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) in the following patients:
1. Affected patients with a relevant cancer for the diagnosis of Lynch syndrome when IHC or MSI is positive; or
3. At-risk relatives (first- or second-degree) of patients with Lynch syndrome with a known MMR mutation; or
4. Patients with a differential diagnosis of attenuated FAP versus MYH-associated polyposis versus Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation; or
5. Patients without colorectal cancer but with a family history meeting these Revised Bethesda or Amsterdam II criteria when no affected family members have been tested for MMR mutations.
   a. Revised Bethesda guidelines
      i. First-degree relative with a Lynch syndrome-related cancer,* with one of the cancers being diagnosed in a patient before the age of 50; or
      ii. Presence of synchronous or metachronous CRC or other Lynch syndrome related cancer, regardless of age; or
      iii. CRC with high microsatellite instability histology diagnosed in a patient less than 60-years old; or
      iv. CRC diagnosed in one or more first-degree relatives with a Lynch syndrome related cancer* with one of the cancers being diagnosed at younger than age 50 years; or
      v. CRC diagnosed in two or more first- or second degree relatives with Lynch related cancer,* regardless of age.
   b. Amsterdam II - (the patient must meet all of the following):
      i. Three or more relatives with an associated Lynch Syndrome-related cancer;*
      ii. One must be a first-degree relative of the other two;
      iii. Two or more successive generations affected;
      iv. At least one of the relatives with cancer associated with Lynch Syndrome was diagnosed before the age of 50;
      v. Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma
      vi. Tumors should be verified by pathologic examination;
**Modifications:**

- EITHER: very small families, which cannot be further expanded, can be considered to have HNPCC with only 2 colorectal cancers in first-degree relatives if at least 2 generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years;
- OR: in families with 2 first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

E. Genetic testing for EPCAM is covered (subject to Limitations/ Exclusions and Administrative Guidelines) when any one of the following 3 major criteria is met:

1. Patients with colorectal cancer, for the diagnosis of Lynch syndrome when:
   a. Tumor tissue shows lack of MSH2 expression by immunohistochemistry and patient is negative for a germline mutation in MSH2; or
   b. Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6; OR
2. At risk relatives of patients with Lynch syndrome with a known EPCAM mutation; OR
3. Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR mutations, and when sequencing for MMR mutations is negative.

F. Genetic testing for BRAF V600E or MLH1 promoter methylation is covered (subject to Limitations/ Exclusions and Administrative Guidelines) to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

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

III. Limitations/Exclusions

A. For this policy, “at-risk relatives” primarily refers to first-degree and in some cases, second-degree relatives.

B. Judgment must be allowed in the case of a small family pedigree when extended family members may need to be included in the testing strategy.

C. It is recommended that, when possible, initial genetic testing for FAP Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the mutation found in the affected family member.

D. HMSA will only cover an affected family member who is enrolled in certain HMSA plans.

E. In many cases, genetic testing for MYH gene mutations should first target the specific mutations Y165C and G382D, which account for the majority of mutations in Caucasian populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

F. For patients with colon, endometrial (under age 50), stomach, bladder, ureter, and renal pelvis, biliary tract, brain (usually glioblastoma), pancreas, sebaceous gland adenomas, keratocanthomas, carcinoma of the small bowel, or ovarian, cancer being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test, or the immunohistochemistry (IHC) test with or without BRAF gene mutation testing, should be used as an initial evaluation of tumor tissue prior to MMR gene analysis. Both tests are not necessary. Consideration of proceeding to MMR gene sequencing would depend on results of MSI or IHC testing. IHC testing in particular may help direct which MMR gene likely contains a mutation, if any, and may also provide some additional information if MMR genetic testing is inconclusive.
G. When indicated, genetic sequencing for MMR gene mutations should begin with \textit{MLH1} and \textit{MSH2} genes unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications; when MMR gene mutations are expected based on IHC or MSI studies but none is found by standard sequencing, additional testing for large deletions or duplications is appropriate.

H. This policy also assumes that the microsatellite instability (MSI) test or the immunohistochemistry (IHC) test as an initial evaluation for Lynch syndrome is performed as part of the routine pathological evaluation of the CRC or endometrial cancer specimen. Thus, this policy deals only with testing for genetic mutations. Consideration of proceeding to DNA mismatch repair (MMR) gene sequencing would depend on results of MSI and IHC testing. The MSI and IHC testing may also provide some additional information when HNPCC genetic testing is inconclusive.

I. Laboratories that conduct genetic testing must be CLIA-certified.

J. Repeat testing is not covered.

K. All references to polyps in this policy are considered to be adenomatous polyps.

IV. Administrative Guidelines

A. Precertification is required for genetic risk assessment and genetic testing:
   1. Unaffected individuals
      a. Genetic risk assessment is considered by HMSA as part of the precertification process to approve genetic testing in unaffected individuals as outlined in Criteria/Guidelines II.B.1 II.D.3., II.D.5.a, and II.D.5.b.
   2. Affected individuals
      a. IHC or MSI testing will be covered without precertification following surgery.
      b. Genetic risk assessment is required for affected individuals with positive test results for IHC or MSI prior to further genetic testing.
      c. Genetic risk assessment is required with precertification for affected individuals for whom IHC or MSI test results are unavailable and who have first or second degree relatives with Lynch-related cancer prior to genetic testing.
      d. Genetic risk assessment is required with precertification for individuals with attenuated familial adenomatous polyposis, familial adenomatous polyposis and MYH associated polyposis.

B. Documentation must specify how the results of genetic testing will impact the clinical management of the patient in terms of improving health outcomes.

C. Services must be conducted in a face-to-face consultation and/or telemedicine consult visit (in accordance with HMSA’s current telemedicine payment policy) and a subsequent consultation letter or report must be submitted to the treating physician.

D. Services must be conducted by a properly certified/licensed and credentialed genetic specialist (i.e., board-certified medical geneticist (MD), board-certified clinical geneticist (PHD), board-certified genetic counselor (MS and/or CGC), or licensed advanced practice registered nurse in genetics (APRN)).

E. One risk assessment visit after genetic testing is covered for patients who qualified for predictive genetic testing as outlined above.

F. To precertify please complete HMSA’s \textbf{Precertification Request} and fax or mail the form as indicated. The information received should include the member’s family history and a brief summary as to why the genetic test is needed.
G. If precertification is not obtained, the member will not be held responsible for payment of denied services unless an Agreement of Financial Responsibility is completed and signed.

**Unaffected** - No personal history of cancer

**Affected** - Personal history of cancer

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<tr>
<th>CPT Codes</th>
<th>Description</th>
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<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>known familial variants</td>
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<td>81203</td>
<td>duplication/deletion variants</td>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81294</td>
<td>duplication/deletion variants</td>
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<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>81298</td>
<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>duplication/deletion variants</td>
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<td>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</td>
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<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>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
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V. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. References