



Genetic Testing for Lynch Syndrome/Colorectal Cancer and Polyposis Syndromes

I. Policy

University Health Alliance (UHA) will reimburse for genetic testing for Lynch syndrome/colorectal cancer and polyposis syndromes when they are determined to be medically necessary and when they meet the medical criteria guidelines (subject to limitations and exclusions) indicated below.

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 adenomatous polyposis coli (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 familial adenomatous polyposis (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 mismatch repair (MMR) mutations depends upon clinical presentation.
- C. Genetic testing for MUTYH 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 mis-match repair (MMR) gene mutations is covered (subject to Limitations/Exclusions and Administrative Guidelines) in the following patients:
 - 1. Affected patients with colorectal cancer for the diagnosis of Lynch syndrome (hereditary nonpolyposis colorectal cancer);
 - 2. Patients with endometrial cancer who were diagnosed at <50 years of age or have one first-degree relative diagnosed with a Lynch associated cancer for the diagnosis of Lynch syndrome.
 - 3. At-risk relatives (first- or second-degree) of patients with Lynch syndrome with a known MMR mutation;
 - 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;
 - 5. Patients without colorectal cancer but with a family history meeting these Revised Bethesda guidelines or Amsterdam II criteria when no affected family members have been tested for MMR mutations.
 - a. Revised Bethesda guidelines:
 - i. Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old; or

- ii. First-degree relative with a Lynch syndrome-related cancer,* with one of the cancers being diagnosed before the age of 50; or
 - iii. Presence of synchronous or metachronous CRC or other Lynch syndrome related cancer*, regardless of age; or
 - iv. CRC with high microsatellite instability histology diagnosed in a patient less than 60-years old; or
 - v. 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
 - vi. CRC diagnosed with one or more first-degree relatives with an HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed at younger than age 50 years, OR CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumor, regardless of age.
- b. Amsterdam II criteria – (the patient must meet all of the following):
- i. Three or more relatives with a Lynch Syndrome-related cancer*
 - One must be a first-degree relative of the other two;
 - Lynch Syndrome-related cancer* involving at least two successive generations;
 - At least one of the relatives with cancer associated with Lynch Syndrome was diagnosed before the age of 50;
 - Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal cancer.
 - 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 two colorectal cancers in first-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 years; or
 - In families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

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

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

1. Patients with colorectal cancer, for the diagnosis of Lynch syndrome (see Policy Guidelines) 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 (see Policy Guidelines) 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 and Administrative Guidelines) to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

NOTE:

This UHA payment policy is a guide to coverage, the need for prior authorization and other administrative directives. It is not meant to provide instruction in the practice of medicine and it should not deter a provider from expressing his/her judgment.

Even though this payment policy may indicate that a particular service or supply is considered covered, specific provider contract terms and/or member individual benefit plans may apply, and this policy is not a guarantee of payment. UHA reserves the right to apply this payment policy to all UHA companies and subsidiaries.

UHA understands that opinions about and approaches to clinical problem may vary. Questions concerning medical necessity (see Hawaii Revised Statutes §432E-1.4) are welcome. A provider may request that UHA reconsider the application of the medical necessity criteria in light of any supporting documentation.

III. Limitations/Exclusions

- A. For this policy, “at-risk relatives” primarily refers to first-degree relatives. However, some judgment must be allowed, for example, in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.
- B. It is recommended that, when possible, initial genetic testing for FAP, attenuated familial adenomatous polyposis (AFAP), MYH associated polyposis, or 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.
- C. 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.
- D. For patients with colorectal 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.
- E. When indicated, genetic sequencing for MMR gene mutations should begin with *MLH1* and *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.

- F. Laboratories that conduct genetic testing must be CLIA-certified.
- G. Repeat testing is not covered.
- H. All references to polyps in this policy are considered to be adenomatous polyps.

IV. Administrative Guidelines

- A. Prior authorization is required for genetic risk assessment and genetic testing.
- B. To request prior authorization, please submit via UHA's online portal. If a login has not been established, you may contact UHA at 808-532-4000 to establish one.
- C. Genetic risk assessment
 - 1. Unaffected individuals (no personal history of cancer)
 - a. Genetic risk assessment is considered by UHA as part of the prior authorization process to approve genetic testing in unaffected individuals as outlined in this policy
 - 2. Affected individuals (personal history of cancer)
 - a. BRAF, IHC or MSI testing will be covered without prior authorization following surgery;
 - b. Genetic risk assessment is required for affected individuals with positive test results for BRAF, IHC or MSI prior to further genetic testing;
 - c. Genetic risk assessment is required with prior authorization 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 prior authorization for individuals with attenuated familial adenomatous polyposis, familial adenomatous polyposis and MUTYH associated polyposis.
 - 3. Documentation should include the member's family history and a brief summary as to why the genetic test is needed. Documentation must specify how the results of genetic testing will impact the clinical management of the patient in terms of improving health outcomes.
 - 4. Services must be conducted in a face-to-face consultation and a subsequent consultation letter or report must be submitted to the treating physician.
 - 5. 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).
 - 6. One risk assessment visit after genetic testing is covered for patients who qualified for predictive genetic testing as outlined above.
- D. Genetic testing
 - 1. Documentation should include the member's family history and a brief summary as to why the genetic test is needed. Documentation must specify how the results of genetic testing will impact the clinical management of the patient in terms of improving health outcomes.

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	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; 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
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

V. Policy History

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