I. Description

Genetic testing is available for both affected individuals, as well as those at risk, for various types of hereditary cancer. This policy describes genetic testing for familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer [HNPCC]), MUTYH-associated polyposis, and Lynch syndrome–related endometrial cancer.

The evidence for genetic testing for the adenomatous polyposis coli (APC) mutation in individuals with a clinical differential diagnosis of attenuated familial adenomatous polyposis (aFAP), MUTYH-associated polyposis and Lynch syndrome, or individuals who are at-risk relatives of patients with FAP, includes a TEC Assessment. Outcomes of interest are overall survival, disease-specific survival, test accuracy and test validity. For patients with an APC mutation, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. A related familial polyposis syndrome, MUTYH-associated polyposis (MAP) syndrome, is associated with mutations in the MUTYH gene. Testing for this genetic mutation is necessary when the differential diagnosis includes both FAP and MAP, because distinguishing between the two leads to different management strategies. In some cases, Lynch syndrome may be part of the same differential diagnosis, depending on presentation. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for MMR mutations in 1) individuals who have a clinical differential diagnosis of attenuated familial adenomatous polyposis (aFAP), MUTYH-associated polyposis and Lynch syndrome, or 2) individuals who have colon cancer, or 3) individuals who have endometrial cancer and 1 first degree relative diagnosed with a Lynch-associated cancer, or 4) individuals who are at-risk relatives of patients with Lynch syndrome, or 5) patients without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, includes an ARHQ report, supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, and an EGAPP recommendation for genetic testing in CRC. Outcomes of interest are overall survival, disease-specific survival, test accuracy and test validity. A chain of indirect evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR mutation, in that counseling has been shown to affect testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-
term, nonrandomized controlled study and 1 cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance versus those who did not. A positive genetic test for an MMR mutation can also lead to changes in management of other Lynch syndrome malignancies. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for EPCAM mutations in patients who have a CRC in which MMR testing is negative for all MMR mutations but who screen positive for microsatellite instability (MSI) and lack MSH2 immunohistochemical evidence of protein expression includes mutation prevalence studies and case series. Outcomes of interest are overall survival, disease-specific survival, test accuracy and test validity. Studies have shown an association between EPCAM mutations and Lynch-like disease in families and the cumulative risk for CRC is similar to carriers of an MSH2 mutation. Identification of an EPCAM mutation could lead to changes in management that lead to improved health outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for BRAF V600E or MLH1 promoter methylation in patients who have CRC but in whom MLH1 protein is not expressed on immunohistochemical analysis includes a few case series. Outcomes of interest are overall survival, disease-specific survival, test accuracy and test validity. Studies have shown, with high sensitivity and specificity, an association of BRAF V600E mutation or MLH1 promoter methylation with sporadic CRC. Therefore, this type of testing could eliminate the need for further genetic testing or counseling for Lynch syndrome. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

II. Criteria/Guidelines

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

B. Genetic testing for APC gene mutations is covered (subject to Limitations and Administrative Guidelines) for the following:
   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. MUTYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations, MUTYH mutations, or screening for MMR mutations depends upon clinical presentation.
   3. Genetic testing for APC gene mutations is not covered for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

C. Genetic testing for MUTYH gene mutations is covered (subject to Limitations and Administrative Guidelines) for patients with a differential diagnosis of attenuated FAP versus MUTYH-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 MUTYH-associated polyposis (autosomal recessive).

D. Genetic testing for mis-match repair (MMR) gene mutations is covered (subject to Limitations and Administrative Guidelines) in the following:
   1. Patients with colorectal cancer for a diagnosis of Lynch syndrome; 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 MUTYH-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 the Revised Bethesda or Amsterdam II criteria when no affected family members have been tested for MMR mutations.

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 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 and Administrative Guidelines) to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

III. Policy Guidelines

Due to the high lifetime risk of cancer of the majority of the genetic syndromes discussed in 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.

It is recommended that, when possible, initial genetic testing for FAP or Lynch syndrome is performed in an affected family member so that testing in unaffected family members can focus on the mutation found in the affected family member (see Benefit Application section).

In many cases, genetic testing for MUTYH gene mutations should first target the specific mutations Y165C and G382D, which account for more than 80% of mutations in Caucasian populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

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. 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.

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 are found by standard sequencing, additional testing for large deletions or duplications is appropriate.
Amsterdam II Clinical Criteria: All criteria must be met. The Amsterdam criteria are the most stringent criteria for defining families at high risk for Lynch syndrome:
- Three or more relatives with an associated Lynch-related cancer*
- One should be a first-degree relative of the other two;
- Two or more successive generations affected;
- One or more relatives diagnosed before the age of 50 years;
- Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma;
- 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.

The Bethesda guidelines are less strict than the Amsterdam II criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also felt to be more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:
- 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
- Presence of synchronous or metachronous CRC or other Lynch syndrome related cancer*, regardless of age; or
- CRC with high microsatellite instability histology diagnosed in a patient less than 60-years old; or
- 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
- 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 bland 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.

*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 keratoacanthomas as seen in Muir-Torre syndrome

IV. Limitations
A. For this policy, “at-risk relatives” primarily refers to first-degree and in some cases, second-degree relatives.
B. Genetic testing is covered only when the testing will impact the clinical management of the patient in terms of improving health outcomes.
C. 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.

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

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

F. In many cases, genetic testing for MUTYH 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.

G. 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.

H. 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.

I. 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.

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

K. Repeat testing is not covered.

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

V. Administrative Guidelines

A. Precertification is required for genetic risk assessment and genetic testing:
   1. Unaffected individuals
   2. 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 and II.D.5 (the Amsterdam II and Revised Bethesda criteria are found on page 4).
   3. Affected individuals
      a. BRAF, 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 BRAF, 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 MUTYH 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 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.

**Affected** - Personal history of cancer

**Unaffected** - No personal history of cancer

<table>
<thead>
<tr>
<th>CPT Codes</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>
</tr>
<tr>
<td>81202</td>
<td>known familial variants</td>
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<tr>
<td>81203</td>
<td>duplication/deletion variants</td>
</tr>
<tr>
<td>81292</td>
<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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<tr>
<td>81293</td>
<td>known familial variants</td>
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<tr>
<td>81294</td>
<td>duplication/deletion variants</td>
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<tr>
<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>known familial variants</td>
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<tr>
<td>81297</td>
<td>duplication/deletion variants</td>
</tr>
<tr>
<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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Genetic Testing for Lynch Syndrome/Colorectal Cancer and Polyposis Syndromes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81299</td>
<td>known familial variants</td>
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<tr>
<td>81300</td>
<td>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 deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
</tr>
<tr>
<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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<tr>
<td>81318</td>
<td>known familial variants</td>
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<tr>
<td>81319</td>
<td>duplication/deletion variants</td>
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<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
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</table>

### VI. 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.

### VII. References