Genetic Testing for Lynch Syndrome
And Other Inherited Colon Cancer Syndromes

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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 [HNPPC]), 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 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-degrees) of patients with FAP and/or a known APC mutation.
   2. Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis (MAP)
      vs. Lynch syndrome. Whether testing begins with APC mutations, or screening for MMR
      mutations depends upon clinical presentation.

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 MAP versus Lynch
syndrome and a negative test result for APC gene mutations. Family history of no parents or
children with FAP is consistent with MAP (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 (see Policy Guidelines); or
2. Patients with endometrial cancer and one first-degree relative diagnosed with a Lynch
associated cancer (see Policy Guidelines) for the diagnosis of Lynch syndrome.
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 MAP 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 (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.

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.

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.

The Amsterdam II Clinical Criteria (all criteria must be met) are the most stringent criteria for defining families at high risk for Lynch syndrome:

- Three or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis)
- 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 Revised Bethesda Guidelines (fulfillment of any criterion meets 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 considered more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old;
- 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. Genetic testing for APC gene mutations is not covered for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.
B. Genetic testing for all other gene mutations for Lynch syndrome or colorectal cancer has not been shown to improve 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. HMSA will only cover an affected family member who is enrolled in certain HMSA plans.
E. Laboratories that conduct genetic testing must be CLIA-certified.
F. Repeat testing is not covered.
G. 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
      a. Genetic risk assessment is considered by HMSA as part of the precertification process to approve genetic testing in unaffected individuals meeting the outlined in Criteria/Guidelines II.B.1, II.D.3, II.D.5., II.E.2 and II.E.5. (the Amsterdam II and Revised Bethesda criteria are found in the Policy Guideline section)
   2. 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

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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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<td>known familial variants</td>
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<tr>
<td>81203</td>
<td>duplication/deletion variants</td>
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<td>81288</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>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>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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<td>Genetic counseling, under physician supervision, each 15 minutes</td>
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**VI. Background**

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

FAP 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 (CRC). Mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP accounts for about 1% of CRC 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. FAP associated with these collective extraintestinal manifestations is sometimes referred to as Gardner syndrome. FAP may also be associated with central nervous system 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 (11307K) has been found in Ashkenazi Jewish descendants, which may explain a portion of the familial CRC occurring in this population.

A subset of FAP patients may have attenuated FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, CRC occurring at an average age of 50 to 55 years, but a high lifetime risk of CRC of about 70% by age 80 years. The risk of extra-intestinal cancer is lower compared with classical FAP but still high at an estimated cumulative lifetime risk of 38% compared with the general population. Only 30% or fewer of attenuated FAP patients have APC mutations; some of these patients have mutations in the MUTYH (formerly MYH) gene and are 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 attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH mutations are associated with a cumulative CRC risk of about 80% by age 70, whereas monoallelic MUTYH mutation-associated risk of CRC appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk CRC 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 by 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 versus MAP versus 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 CRC and other malignancies as a result of an inherited mutation in a DNA *MMR* gene. Lynch syndrome includes those with an existing cancer and those who have not yet developed cancer. The term HNPCC originated before 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 clarity and analysis, 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 CRC and is 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 CRC 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 CRC 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*, *PMS1*, and *EXO1*. 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 1 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 extracolonic cancers in childhood (eg, brain tumors, leukemias, lymphomas). Those unaffected or surviving early malignancies are at high risk of later CRC (average age of CRC diagnosis, 16.4 years). Family history may not suggest Lynch syndrome. Before cancer diagnosis, patients may have multiple adenomatous polyps and thus may have an initial differential diagnosis of attenuated FAP versus MAP 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 MSI; they result in an MSI-high tumor phenotype. MSI testing was standardized subsequent to a 2004 National Cancer Institute workshop. 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 CRCs are 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 not detected by sequencing of the protein coding regions. Thus IHC may provide additional information.

The BRAF gene is often mutated in CRC 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 CRC in IHC MLH1-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 CRC 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 CRC.
- Patients with a differential diagnosis of Lynch syndrome vs. attenuated FAP versus MAP.
- Lynch syndrome patients. Genetic testing of the proband with CRC 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.

Distinct from patients with EPCAM deletions, rare cases of Lynch syndrome have been reported without detectable germline MMR mutations although IHC testing demonstrated 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 be in conjunction with a linked genetic alteration near the affected MMR gene. The germline epimutations may arise de novo or may be heritable in Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic CRC 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 help in exceptional cases.

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 \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2} have an estimated 40\% to 62\% lifetime risk of developing endometrial cancer, as well as a 4\% to 12\% lifetime risk of ovarian cancer.

**VII. Rationale**

**Familial Adenomatous Polyposis Genetic Testing**

The evidence review for familial adenomatous polyposis (FAP) genetic testing was originally based on a 1998 TEC Assessment, which offered the following conclusions:

- Genetic testing for FAP may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.
- At-risk subjects are considered to be those with greater than 10 adenomatous polyps; or close relatives of patients with clinically diagnosed FAP or of patients with an identified adenomatous polyposis coli (\textit{APC}) mutation.
- The optimal testing strategy is to define the specific genetic mutation in an affected family member and then test the unaffected family members to see if they have inherited the same mutation.

The additional information on attenuated FAP and on \textit{MUTYH}-associated polyposis (MAP) diagnostic criteria and genetic testing is based on information from \textit{GeneReviews} and from several publications that build on prior, cited research. In addition, \textit{GeneReviews} summarized clinical FAP genotype- phenotype correlations that could be used to determine different patient management strategies. The authors of the review concluded, however, that there is no agreement yet about using such correlations to direct management choices.

Testing for the \textit{APC} gene mutation (ie, testing for FAP) is not considered necessary in those with classical FAP, because the genetic testing is not needed to make the diagnosis of FAP in these patients. Testing for the \textit{APC} mutation has no role in the evaluation, diagnosis, or treatment of these patients where the diagnosis and treatment are based on the clinical presentation.

**Lynch Syndrome and Colorectal Cancer Genetic Testing**

The evidence for Lynch syndrome genetic testing in patients with colorectal cancer (CRC) is based on an evidence report published by the Agency for Healthcare Research and Quality (AHRQ), a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, and an EGAPP recommendation for genetic testing in CRC. Based on the AHRQ report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for \textit{MMR} mutations in patients already diagnosed with CRC:

- Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for \textit{MMR} mutation testing and should not be used as a sole determinant or screening test.
- MSI [microsatellite instability] and IHC [immunohistochemical] screening tests for \textit{MMR} mutations have similar sensitivity and specificity. MSI screening has a sensitivity of about 89\% for \textit{MLH1} and \textit{MSH2} and 77\% for \textit{MSH6} and a specificity of about 90\% for all. It is likely that,
using high-quality MSI testing methods, these parameters can be improved. IHC screening has a sensitivity for \( MLH1, MSH2, \) and \( MSH6 \) of about 83% and a specificity of about 90% for all.

- Optional \( BRAF \) testing can be used to reduce the number of patients, who are negative for \( MLH1 \) expression by IHC, needing \( MLH1 \) gene sequencing, thus improving efficiency without reducing sensitivity for \( MMR \) mutations.
- A chain of indirect evidence can be constructed for the clinical utility of testing all patients with CRC for \( MMR \) mutations.
  1. The 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.
  2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. About half of relatives received counseling, and 95% of these chose \( MMR \) gene mutation testing. Among those positive for \( MMR \) gene mutations, uptake of colonoscopic surveillance beginning at age 20 to 25 years was high at 53% to 100%.
    - 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.
    - Surveillance, prevention for other Lynch syndrome cancers.
  3. The chain of evidence from descriptive studies and expert opinion is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (ie, cancer index patient).
    - Subtotal colectomy is recommended as an alternative to segmental resection, but has not been shown superior in follow-up studies
    - Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.
    - Surveillance, prevention for other Lynch syndrome cancers:
      - While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In 1 retrospective study, women who chose this option had no gynecologic cancer over 10 years, whereas about one third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer
      - In 1 study, surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown. Transvaginal ultrasound (TVUS) is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, TVUS in conjunction with endometrial biopsy has been recommended for surveillance.
iii. Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supportive evidence.

Based on an indirect chain of evidence with adequate evidence of benefit to unaffected family members found to have Lynch syndrome, the EGAPP Working Group recommended testing all patients with CRC for MMR gene mutations. Further support for universal testing of CRC patients for MMR gene mutations was reported by Moreira et al in 2012 in a comparison of universal testing of CRC patients to alternative screening approaches. The alternative screening approaches included using the Bethesda guidelines, the Jerusalem recommendations, and a selective strategy including only those diagnosed with CRC before age 70, or after age 70 if meeting the Bethesda guidelines. In the analysis of 10,206 newly diagnosed CRC patients from 4 large cohort studies, MSI testing was used in 2150 patients and immunostaining was used in 2278 patients, while both MSI and immunostaining were used in 5591 patients. MMR gene mutations were found in 312 (3.1%) patients overall. The universal screening approach was superior to the other screening approaches in the population-based cohorts (n=3671 probands), with a sensitivity of 100% (95% confidence interval [CI], 99.3% to 100%), specificity of 93% (95% CI, 92.0% to 93.7%), and diagnostic yield of 2.2% (95% CI, 1.7% to 2.7%). The Bethesda guidelines screening sensitivity was 87.8% (95% CI, 78.9% to 93.2%), with a specificity of 97.5% (95% CI, 96.9 to 98.0%) and a diagnostic yield of 2.0% (95% CI, 1.5% to 2.4%; p<0.001). The screening sensitivity with the Jerusalem recommendations was 85.4% (95% CI, 77.1% to 93.6%), with a specificity of 96.7% (95% CI, 96.0% to 97.2%) and a diagnostic yield of 1.9% (95% CI, 1.4% to 2.3%; p<0.001). The selective strategy had a sensitivity of 95.1% (95% CI, 89.8% to 99.0%), with a specificity of 95.5% (95% CI, 94.7% to 96.1%) and a diagnostic yield of 2.1% (95% CI, 1.6% to 2.6%; p<0.001). However, the diagnostic yield differences between the screening approaches were small, and the false-positive yield was 2.5% with universal screening. In the selective strategy, 34.8% fewer patients required tumor MMR testing and 28.6% fewer required analyses of MMR mutations, resulting in 4.9% missed Lynch syndrome cases.

In addition to DNA mismatch repair (MMR) gene mutation testing, evidence now supports testing for EPCAM deletions in particular cases where all MMR gene mutation testing is negative, but tumor MSH2 IHC indicates lack of expression, and tumor MSI testing shows a high level of instability. EPCAM is found just upstream, in a transcriptional sense, of MSH2. Deletions of EPCAM that encompass the last 2 exons of the EPCAM gene, including the polyadenylation signal that normally ends transcription of DNA into messenger RNA, result in transcriptional “read-through” and subsequent hypermethylation of the nearby and downstream MSH2 promoter. This hypermethylation prevents normal MSH2 protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an MSH2 mutation prevents MSH2 gene expression. Several studies have characterized such EPCAM deletions, established their correlation with the presence of EPCAM-MSH2 fusion messenger RNAs (apparently nonfunctional) and with the presence of MSH2 promoter hypermethylation, and, most importantly, have shown the cosegregation of these EPCAM mutations with Lynch-like disease in families. Because studies differ slightly in how patients were selected, prevalence of these EPCAM mutations is difficult to estimate but may be in the range of 20% to 40% of patients/families who meet Lynch syndrome criteria, do not have an MMR mutation, but have MSI-high tumor tissue. Kempers et al reported that carriers of an EPCAM deletion had a 75% (95% CI, 65% to 85%) cumulative risk of CRC by age 70 years, which did not differ significantly different from that of carriers of an MSH2 deletion (77%; 95% CI, 64% to 90%); mean age at diagnosis
was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0% to 27%) by age 70 compared with carriers of a MSH2 mutation (51%; 95% CI, 33% to 69%; p<0.001).

Grandval et al selected 25 patients with tumors exhibiting complete loss of MSH2 protein but without a point mutation or genomic rearrangement of the MSH2 gene and found 7 cases of a deletion of the 3 prime exon of EPCAM. Genetic testing was subsequently performed on 25 adult first-degree relatives of the 7 cases, and 12 relatives were found to be deletion carriers. Six additional relatives had died from Lynch-associated tumors, and 5 were obligate carriers. In summary, the risk to develop CRC was high, 93.1% (27/29) in deletion carriers older than 30 years of age.

Although MMR gene sequencing of all patients is the most sensitive strategy, it is highly inefficient, cost-ineffective, and not recommended. Rather, a screening strategy of MSI or IHC testing (with or without optional BRAF testing) is recommended and retains a relatively high sensitivity. Some evidence suggests that IHC requires particular training and experience. Although a particular strategy was not recommended by the EGAPP Working Group, several are potentially effective; efficiency and cost-effectiveness may depend on local factors.

In 2010, Bouzourene et al analyzed MLH1 protein abnormalities in 11 patients with sporadic CRC and 16 patients with Lynch syndrome. BRAF mutation was not found in any of the Lynch syndrome patients. MLH1 promoter methylation was only present in 1 Lynch syndrome patient. However, 8 of the 11 sporadic CRC patients had the BRAF mutation, and all 11 patients were MLH1 methylated, suggesting patients with BRAF mutations could be excluded from germline testing for Lynch syndrome. In 2013, Jin et al evaluated MMR proteins in 412 newly diagnosed CRC patients. MLH1 and PMS2 protein stains were absent in 65 patients who were subsequently tested for BRAF mutation. Thirty-six (55%) of the 65 patients had the BRAF V600E mutation, thus eliminating the need for further genetic testing or counseling for Lynch syndrome.

In 2013, Capper et al reported on a technique of V600E IHC testing for BRAF mutations on a series of 91 stratified as high MSI CRC patients. The authors detected BRAF-mutated CRC with 100% sensitivity and 98.8% specificity. V600E positive lesions were detected in 21% of MLH1-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore, V600E IHC testing for BRAF could be an alternative to MLH1 promoter methylation analysis.

To summarize, BRAF V600E mutation or MLH1 promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH protein expression. The presence of BRAF V600E or absence of MLH1 protein expression due to MLH1 promoter methylation rarely occurs in Lynch syndrome and would eliminate the need for further germline mutation analysis for a Lynch syndrome diagnosis.

Previous recommendations have used family history as an initial screen to determine who should proceed to MMR laboratory testing. Family history is important for counseling families, but, based on this and similar evidence, it is not recommended as an initial screening tool for decisions about testing patients who already have CRC. Recent studies have shown that limiting laboratory testing to patients who met even the more sensitive Revised Bethesda criteria (ie, vs the Amsterdam II criteria) would have missed as many as 28% of Lynch syndrome cases. However, the Amsterdam II or Revised Bethesda criteria may be used in identifying those without CRC who might be tested.

Limiting testing for Lynch syndrome on the basis of age (eg, testing only patients <50 years) is also not recommended. For example, Hampel et al found that, among 18 Lynch syndrome patients from a sample of 500 unselected CRC patients, only 8 (44%) patients were diagnosed at age younger than 50 years. Similarly, Canard et al reported that restricting screening to patients younger than 50 years
would have missed about half of patients eventually found to have Lynch syndrome. Another group screened CRC patients younger than age 60 and identified 98 likely (MSI-positive, BRAF-negative) Lynch syndrome cases; of these, 47% were between 50 and 60 years of age. A large study of Lynch syndrome families found that the cumulative risk of CRC in MMR mutation carriers was only 13% (95% CI, 9% to 19%) by age 50, but 35% (95% CI, 25% to 49%) by age 70. For MSH6 mutation carriers, however, CRC risk do not appear to increase until after age 60.

The estimated risk of stomach cancer in a large study of Lynch syndrome families was 6% (95% CI, 0.2% to 17%) for carriers of MLH1 mutations and warrants further study to address the utility of gastric surveillance.

As the EGAPP recommendations noted, current evidence is insufficient to clearly support benefit from genetic testing to the index patient with CRC if found to have Lynch syndrome. However, professional societies have reviewed the evidence and concluded that genetic testing likely has direct benefits for at least some patients with CRC and Lynch syndrome on the basis of differing recommendations for postsurgical surveillance, and for those who choose prophylactic surgical treatment instead of surveillance.

In the absence of preventive surgery, heightened surveillance is recommended. The National Comprehensive Cancer Network (NCCN) guidelines for colon cancer and for CRC screening recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year postsurgery and, if normal, again in 3 years, then every 5 years based on findings. However, because of the high likelihood of cancer, colonoscopy is recommended every 1 to 2 years throughout life for patients with Lynch syndrome before cancer diagnosis; and the high likelihood of a second primary cancer is based on a first cancer diagnosis. NCCN guidelines on genetic/familial high-risk assessment for colorectal indicate for MLH1, MSH2, and EPCAM mutation carriers that surveillance with colonoscopy should begin “at age 20 to 25 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years. “MSH6 mutation carriers should begin surveillance with colonoscopy at age 30 to 35 years, and PMS2 carriers should begin surveillance at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 years for MSH6 and PMS2 mutation carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years.” “If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered.”

Early documentation of the natural history of CRC in highly selected families with a strong history of hereditary CRC indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively, in those with CRC. As a result, in 1996, the Cancer Genetic Studies Consortium recommended that if CRC is diagnosed in patients with an identified mutation or a strong family history, a subtotal colectomy with ileorectal anastomosis (IRA) should be considered as an option to segmental resection. Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. One study suggested that subtotal colectomy with IRA markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance. A mathematical model comparing total colectomy and IRA to hemicolection estimated increased life expectancies of 2.3, 1, and 0.3 years for ages 27, 47, and 67, respectively; for
stage 1 cancer, estimated life expectancies for the same ages were 3.4, 1.5, and 0.4, respectively. Based on this work, the joint American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) review of risk-reducing surgery in hereditary cancers recommended offering both options to the patient with Lynch syndrome and CRC, especially those who are younger. This ASCO/SSO review also recommended offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch anal anastomosis or anterior proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

Lynch Syndrome and Endometrial Cancer Genetic Testing

Several groups have recommended screening endometrial cancer patients for Lynch syndrome. At the 2010 Jerusalem Workshop on Lynch Syndrome, it was proposed that all incident cases of endometrial cancer be screened for Lynch syndrome using mismatch repair-immunohistochemical (MMR-IHC) testing. Clarke and Cooper noted that Sloan-Kettering Cancer Center screens all patients younger than 50 years of age with endometrial cancer using MMR-IHC, as well as patients older than 50 years with suggestive tumor morphology, lower uterine segment (LUS) location, personal/family history, or synchronous cell carcinoma of the ovary. Kwon et al recommended MMR-IHC screening of women with endometrial cancer at any age who have at least 1 first-degree relative with a Lynch syndrome–associated cancer.

The risk of endometrial cancer in MMR mutation carriers has been estimated at 34% (95% CI, 17% to 60%) by age 70, and at 8% for ovarian cancer (95% CI, 2% to 39%) by age 70. Risks do not appear to appreciably increase until after age 40.

In a 2012 prospective study, 179 consecutive endometrial cancer patients 70 years of age or younger were analyzed for MSI, using IHC for expression of 4 MMR proteins, MMR gene methylation status, and BRAF mutations. Results are presented in Table 1; 92% of patients were older than 50 years of age.

### Table 1. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome

<table>
<thead>
<tr>
<th>Result</th>
<th>N</th>
<th>Percent (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsatellite stable and normal protein staining</td>
<td>137</td>
<td>76%</td>
</tr>
<tr>
<td>MSI-H and MLH1 absent</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Sporadic MSI-H</td>
<td>31</td>
<td>17% (13% to 24)</td>
</tr>
<tr>
<td>Likely to have Lynch syndrome</td>
<td>11</td>
<td>6% (3% to 11%)</td>
</tr>
<tr>
<td>Mutation-positive</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No mutation found</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Refuses further DNA testing</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Another study examined 625 endometrial cancer patients who underwent hysterectomy; endometrial cancer was classified as LUS in 9 patients. Twenty-seven randomly chosen patients from the non-LUS group were compared with the LUS group, and no statistically significant differences were found between groups for MSI status or IHC findings. The incidence of Lynch syndrome in the LUS group was 1 in 9.

Kwon et al developed a Markov Monte Carlo simulation model to compare 6 strategies for Lynch syndrome testing in women with endometrial cancer. Overall, the results suggested that IHC triage of women at any age who have at least 1 first-degree relative with a Lynch-associated cancer was the most cost-effective strategy (incremental cost-effectiveness ratio, $9126) for identifying Lynch
syndrome and subsequent CRC cases. The model used published prevalence estimates of Lynch syndrome in all endometrial cancer patients of 2% (range, 1%-3%), and of 17% (range, 15%-20%) in endometrial cancer patients with at least 1 first-degree relative with a Lynch-associated cancer. Results are presented in Table 2.

Table 2. Modeling of Endometrial Cancer Screening Strategies for Detecting Lynch Syndrome

<table>
<thead>
<tr>
<th>Testing Strategy</th>
<th>No. Cases Subject to IHC Triage</th>
<th>No. Identified With Lynch Syndrome</th>
<th>No. Subsequent CRC Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam II criteria</td>
<td>NA</td>
<td>539</td>
<td>2582</td>
</tr>
<tr>
<td>Age &lt;50 y, and at least 1 FDR (Lynch-associated cancer)</td>
<td>NA</td>
<td>530</td>
<td>2470</td>
</tr>
<tr>
<td>IHC triage &lt;age 50 y</td>
<td>6285</td>
<td>520</td>
<td>2442</td>
</tr>
<tr>
<td>IHC triage &lt;age 60 y</td>
<td>16,226</td>
<td>548</td>
<td>2450</td>
</tr>
<tr>
<td>IHC triage at any age; at least 1 FDR with Lynch-associated cancer</td>
<td>5786</td>
<td>755</td>
<td>2442</td>
</tr>
<tr>
<td>IHC triage all endometrial cancers</td>
<td>45,000</td>
<td>827</td>
<td>2413</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; FDR: first-degree relative; IHC: immunohistochemical; NA: not available.

Female patients with Lynch syndrome who choose risk-reducing surgery are encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. As noted, in 1 retrospective study, women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer. In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome. This study also estimated that, for every 100 women diagnosed with Lynch syndrome–associated CRC, about 23 will be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Recent data on mutation-specific risks suggest that prophylactic gynecologic surgery benefits for carriers of MSH6 mutations may offer less obvious benefits compared with harms, because the lifetime risk of endometrial cancer is lower than for carriers of MLH1 or MSH2 mutations, and the lifetime risk of ovarian cancer is similar to the risk for the general population.

However, for carriers of the EPCAM deletion, 3 recent studies found 3 cases of endometrial cancer in 103 female carriers who did not undergo preventative hysterectomy. Women with EPCAM deletions consequently have a 1-fold lower lifetime risk of developing endometrial cancer than with carriers with the MMR mutation. This might support a clinical management scenario rather than prophylactic surgery. An alternative to prophylactic surgery is surveillance for endometrial cancer using TVUS and endometrial biopsy. Evidence indicates that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet indicates surveillance reduces mortality due to endometrial cancer. Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>NCT01447199</td>
<td>The Molecular Predisposition to Hereditary Nonpolyposis Colon Cancer (HNPCC)</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>NCT01850654</td>
<td>Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome</td>
<td>4000</td>
</tr>
</tbody>
</table>
Summary of Evidence

The evidence for genetic testing for the APC mutations in individuals who have a clinical differential of attenuated familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), and Lynch syndrome, or at-risk relatives of patients with FAP includes a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and 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, 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 2 leads to different management strategies. Depending on presentation, Lynch syndrome may be part of the same differential diagnosis. 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 FAP, MAP, and Lynch syndrome, or (2) individuals who have colon cancer, or (3) individuals who have endometrial cancer and a 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 Agency for Healthcare Research and Quality report, a 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 colorectal cancer (CRC). Relevant outcomes are overall survival, disease-specific survival, and test accuracy and 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 influence 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 and did not follow recommended colonic surveillance. 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 individuals who have CRC in which MMR testing is negative for all MMR mutations but who screen positive for microsatellite instability and lack MSH2 immunohistochemical evidence of protein expression includes mutation prevalence studies and case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and 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 improve 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 \textit{BRAF} V600E or \textit{MLH1} promoter methylation in individuals who have CRC but in whom MLH1 protein is not expressed on immunohistochemical analysis includes a few case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association of \textit{BRAF} V600E mutation or \textit{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.

\section*{Supplemental Information}

\subsection*{National Comprehensive Cancer Network}

National Comprehensive Cancer Network (NCCN) guidelines for genetic/familial high-risk assessment of colorectal cancer (CRC) recommend 2 approaches to Lynch syndrome mutation screening: (1) all newly diagnosed CRC or (2) all CRC patients diagnosed before age 70 plus those diagnosed at ages 70 and older who meet Bethesda guidelines. Additionally, the guidelines recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years. These guidelines note IHC and sometimes MSI testing may be performed at some centers on all newly diagnosed colorectal and endometrial cancer patients to determine need for genetic testing for Lynch syndrome mutations regardless of family history. The guidelines note “evidence has shown 3 deletions in the \textit{EPCAM} gene, which lead to hypermethylation of the \textit{MSH2} promoter and subsequent \textit{MSH2} silencing, are an additional cause of Lynch syndrome.” Genetic testing is recommended for at-risk family members of patients with positive mutations in \textit{MLH1, MSH2, MSH6, or PMS2}. NCCN guidelines also indicate \textit{BRAF} V600E testing or \textit{MLH1} promoter methylation testing may be used when \textit{MLH1} is not expressed in the tumor on IHC analysis to exclude a diagnosis of Lynch syndrome. As noted in the NCCN guidelines: “the presence of a \textit{BRAF} mutation indicates MLH1 expression is downregulated by somatic methylation of the promoter region of the gene and not by germline mutation.” These guidelines also address FAP (classical and attenuated), and MAP, consistent with the information in this evidence review.

NCCN guidelines for colon cancer recommend colon cancer patients 70 years or younger plus those older than 70 years of age who meet the Bethesda guidelines be tested for the MMR protein for possible Lynch syndrome. The colon cancer guidelines also indicate all colon cancer patients should be questioned about family history and considered for risk assessment as per NCCN colorectal screening guidelines. NCCN guidelines on uterine neoplasms indicate all endometrial cancer patients, especially those younger than 50 years, should be considered for testing for genetic mutations such as Lynch syndrome.

\subsection*{American College of Gastroenterology}

The American College of Gastroenterology (ACG) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.

\section*{Lynch syndrome (LS)}

- “All newly diagnosed colorectal cancers should be evaluated for mismatch repair deficiency.
- “Analysis may be done by immunohistochemical (IHC) testing for the \textit{MLH1/MSH2/MSH6/PMS2} proteins and/or testing for microsatellite instability; tumors that
demonstrate loss of \textit{MLH1} should undergo BRAF testing or analysis for \textit{MLH1} promoter hypermethylation.

- “Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF mutation or hypermethylation of \textit{MLH1}), a known family mutation associated with LS, or a risk of \(\geq 5\%\) chance of LS based on risk prediction models should undergo genetic evaluation for LS.
- “Genetic testing of patients with suspected LS should include germline mutation genetic testing for the \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, and/or \textit{EPCAM} genes or the altered gene(s) indicated by IHC testing.”

\textit{Adenomatous polyposis syndromes}

“\textit{Familial adenomatous polyposis (FAP)}/\textit{MUTYH-associated polyposis/attenuated polyposis}"

- “Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes.
- “Genetic testing of patients with suspected adenomatous polyposis syndromes should include \textit{APC} and \textit{MUTYH} gene mutation analysis.“

\textbf{European Society for Medical Oncology}

The European Society for Medical Oncology (ESMO) published clinical practice guidelines for familial CRC risk in 2010. These guidelines addressed Lynch syndrome, FAP, and MAP. No specific recommendations were made regarding how to initially identify Lynch syndrome cases; several methods, including clinical criteria and universal screening of all CRC cases, were mentioned. Other ESMO recommendations are consistent with the information in this evidence review.

\textbf{American Society of Clinical Oncology and Society of Surgical Oncology}

The American Society of Clinical Oncology and the Society of Surgical Oncology have recommended offering prophylactic total abdominal hysterectomy to female patients with CRC who have completed childbearing or to women undergoing abdominal surgery for other conditions, especially when there is a family history of endometrial cancer. This recommendation was based on the high rate of endometrial cancer in mutation-positive individuals and the lack of efficacy of screening.

\textbf{U.S. Preventive Services Task Force Recommendations}

No U.S. Preventive Services Task Force recommendations for genetic testing of Lynch syndrome and other inherited colon cancer syndromes have been identified.

\textbf{Medicare National Coverage}

Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (ie, clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. Centers for Medicare and Medicaid Services (CMS) recognizes Lynch syndrome as “an autosomal dominant syndrome that accounts for about 3\% to 5\% of colorectal cancer cases. [Lynch] syndrome mutations occur in the
following genes: hMLH1, hMSH2, hMSH6, PMS2, and EPCAM.” CMS also recognizes FAP and MAP syndromes and their associated mutations.

VIII. 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.

IX. References


41. Van Dalen R, Church J, McGannon E, et al. Patterns of surgery in patients belonging to