Protocol

Genetic Testing for FAP and Lynch Syndrome

(20408)

Medical Benefit		**Effective Date**: 01/01/17	**Next Review Date**: 09/18
Preauthorization	Yes	**Review Dates**: 01/10, 01/11, 01/12, 01/13, 01/14, 01/15, 01/16, 09/16, 09/17	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are suspected of attenuated FAP, MAP and Lynch Syndrome, or at-risk relatives of patients with FAP	Interventions of interest are: • Genetic testing for APC	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are suspected of attenuated FAP, MAP and Lynch Syndrome	Interventions of interest are: • Genetic testing for MUTYH after a negative APC test result	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • With suspected attenuated FAP, MAP, and Lynch Syndrome; CRC; or endometrial cancer and first-degree relative with Lynch	Interventions of interest are: • Genetic testing for MMR genes	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are at-risk relatives of patients with Lynch or family history meeting appropriate criteria, but do not have CRC	Interventions of interest are: • Genetic testing for MMR genes	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who warrant Lynch testing, screen negative on MMR testing, but positive for MSI and lack MSH2 protein expression	Interventions of interest are: • Genetic testing for EPCAM variants	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • With CRC in whom MLH1 protein is not expressed on	Interventions of interest are: • Genetic testing for	Comparators of interest are: • No genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival

Populations	Interventions	Comparators	Outcomes
immunohisto-chemical analysis	BRAF V600E or MLH1 promoter methylation		• Test accuracy • Test validity

CRC: colorectal cancer; FAP: familial adenomatous polyposis; MAP: MUTYH-associated polyposis; MMR: mismatch repair; MSI: microsatellite instability.

Description

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

Summary of Evidence

For individuals who are suspected of attenuated FAP, MUTYH-associated polyposis (MAP), and Lynch syndrome, or are at-risk relatives of patients with FAP who receive genetic testing for APC, the evidence includes a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. For patients with an APC variant, 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 variants in the MUTYH gene. Testing for this genetic variant is necessary when the differential diagnosis includes both FAP and MAP because distinguishing between the two leads to different management strategies. Depending on presentation, Lynch syndrome may be part of the same differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, or (2) have colon cancer, or (3) have endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, or (4) are at-risk relatives of patients with Lynch syndrome, or (5) are without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria who receive genetic testing for MMR genes, the evidence 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 Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in CRC. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A chain of 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 variant in an MMR gene, 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 a cohort study of Lynch syndrome family members found significant reductions in CRC among those who did and did not follow recommended colonic surveillance. A positive genetic test for an MMR variant can also lead to changes in the management of other Lynch syndrome malignancies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who warrant Lynch testing, screen negative on MMR testing, but positive for microsatellite instability and lack MSH2 protein expression who receive genetic testing for EPCAM variants, the evidence includes variant 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 variants and Lynch-like disease in families, and the cumulative risk for CRC is similar to carriers of an MSH2 variant. Identification of

an EPCAM variant could lead to changes in management that improve health outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CRC in whom MLH1 protein is not expressed on immunohistochemical analysis who receive genetic testing for BRAF V600E or MLH1 promoter methylation, the evidence 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 between BRAF V600E variant and 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 that the technology results in a meaningful improvement in the net health outcome.

Policy

Genetic Testing for FAP

- Genetic testing for Familial Adenomatous Polyposis (FAP) by testing for APC gene variants may be considered **medically necessary** in ANY of the following:
  - Individuals with greater than 20 colonic polyps; OR
  - First-degree relatives of individuals with FAP or attenuated familial adenomatous polyposis (AFAP) and/or a known APC variant. Exceptions may be necessary in the case of a small family pedigree.
- Genetic testing for Familial Adenomatous Polyposis (FAP) by testing for *MUTYH* gene variants may be considered **medically necessary** in ANY of the following:
  - Individuals with personal history of adenomatous polyposis who have negative APC variant testing and a negative family history for adenomatous polyposis; OR
  - Individuals with personal history of adenomatous polyposis whose family history is positive only for sibling(s); OR
  - Asymptomatic siblings if his/her sibling has a known MYH polyposis; OR
  - History of Desmoid tumor.

Genetic Testing for Lynch Syndrome (see Policy Guidelines for recommended testing protocol*)

- Genetic testing for MMR gene variants in MLH1 and MSH2 genes to determine the carrier status or diagnosis of Lynch syndrome is considered **medically necessary** in ANY of the following:
  - Individuals with colorectal cancer; OR
  - Individuals with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer; OR
  - Individuals without colorectal cancer but who have a first- or second-degree relative with a known MMR variant; OR
  - At-risk relatives of Individuals with Lynch syndrome with a known MMR variant; OR
  - Individuals without colorectal cancer determined to be at high risk when no affected family members have been tested for MMR variants. High risk is defined as meeting either Amsterdam II or Revised Bethesda Guidelines or with ≥ 5% risk of LS on MMRpro, PREMM, or MMRpredict, the accepted computer prediction models.

- Genetic testing for MSH6 and/or PMS2 gene variants may be considered **medically necessary** in high risk Individuals who do not have variants in either the MLH1 or MSH2 genes with ANY of the following:
  - Individuals with colorectal cancer whose screening for MSI or IHC is positive but MLH1 or MSH2 are normal; OR
  - Targeted variant MSH6 and/or PMS2 testing is established for family members (up to third-degree) of individuals with Lynch syndrome with an identified MSH6 and/or PMS2 gene variant; OR
  - Individuals with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer who do not have variants in either the MLH1 or MSH2 genes.
- Genetic testing for EPCAM variants may be considered **medically necessary** in individuals with colorectal cancer whose:
  - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in MSH2, MLH1, PMS2, and MSH6; OR
  - Tumor tissue shows lack of *MSH2* expression by immunohistochemistry AND
    - Individual is negative for a germline variant in MSH2, MLH1, PMS2, and MSH6; OR
    - At-risk relatives of individuals with Lynch syndrome with a known EPCAM variant.
- Genetic testing for BRAF V600E variants or *MLH1* promoter methylation may be considered **medically necessary** to exclude a diagnosis of Lynch syndrome when *MLH1 protein* is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

Genetic Testing for FAP by testing for the APC gene variant in those with FAP diagnosed by clinical criteria is considered **not medically necessary**.

Genetic Testing for Lynch Syndrome using panels, total genome or total exome sequencing using next generation sequencing is considered **investigational**.

Genetic testing for all other gene variants for Lynch syndrome or colorectal cancer is considered **investigational**.

Policy Guidelines

Due to the high lifetime risk of cancer of most genetic syndromes discussed in this protocol, “at-risk relatives” primarily refers to first-degree relatives. However, some judgment must be allowed, e.g., 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 be performed in an affected family member so that testing in unaffected family members can focus on the mutvariantation found in the affected family member.

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

Note: Initial testing on tumor tissue should be either the MSI test, or the immunohistochemistry (IHC) test with or without BRAF gene variant testing 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 variant, if any, and may also provide some additional information if MMR genetic testing is inconclusive.

When indicated, genetic sequencing for MMR gene variants 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 variants are expected based on IHC or MSI studies but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

Several Clinical Laboratory Improvement Amendments (CLIA)-licensed clinical laboratories offer MMR gene variant testing for Lynch syndrome. For example, the GeneTests website, available online at: (http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2622?db=genetests) lists 32 U.S.-located laboratories that offer this service. In at least one laboratory, Lynch syndrome variant testing is packaged under one copyrighted name. The COLARIS test from Myriad Genetic Laboratories includes sequence analysis of MLH1, MSH2, MSH6 and PMS2; large rearrangement analysis for MLH1, MSH2, PMS2, and MSH6 large deletions/ duplications; and analysis for large deletions in the EPCAM gene near MSH2. Note that there are two versions of this test, the COLARIS (excludes *PMS2* testing) and COLARIS Update (includes *PMS2* testing). Individualized tested (e.g., targeted testing for a family variant) can also be requested. The COLARIS®PLUS test includes full sequence analysis of MLH1, MSH2, MSH6, PMS2, and MYH genes and rearrangement analysis of MLH1, MSH2, MSH6, MYH, and EPCAM by microarray comparative genomic hybridization analysis, and multiplex ligation-dependent probe amplification analysis for PMS2.

Similarly, GeneTests lists U.S.-based CLIA-licensed clinical laboratories that provide APC variant testing and those that provide MUTYH variant testing. The COLARIS® AP test (Myriad Genetic Laboratories) includes DNA sequencing analysis of the *APC* and *MUTYH* genes as well as analysis of large rearrangements in the *APC* gene that are not detected by DNA sequencing.

Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent criteria for defining families at high risk for Lynch Syndrome (Vasen et al, 1999):

- 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.

Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families (Umar et al, 2004). 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:

- CRC diagnosed in a patient who is less than 50 years old;
- Presence of synchronous or metachronous CRC or other HNPCC-associated tumors*, regardless of age;

- CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old;
- CRC diagnosed in one or more first-degree relatives with a Lynch syndrome-associated tumor, with one of the cancers being diagnosed at less than 50 years of age;
- CRC diagnosed in two or more first or second-degree relatives with HNPCC-related tumors,* regardless of age.

* HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous gland adenomas and kerato-acanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The inter-pretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

For Medicare Advantage, the above criteria apply but only for the member if they are personally afflicted by a colorectal cancer. Also for the tests to be considered **medically necessary** the results must be intended to be used in the management of the member, such as to determine the extent of surgical treatment, a change in surveillance schedule or other therapeutic management.

Testing of unaffected family members or other individuals is screening and **not medically necessary**.

Background

Currently, two types of hereditary colorectal cancers are well-defined: FAP and Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer [CRC]). 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 CRC. The 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 collec-tive 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 variants in the APC gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Variants in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. A specific APC gene variant (*I1307K*) has been found in subjects of Ashkenazi Jewish descent, which may explain a portion of the familial CRC occurring in this population.

A subset of FAP patients may have attenuated FAP (AFAP), typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, 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.[1] Only 30% or fewer of AFAP patients have APC variants; some of these patients instead have variants in the MUTYH gene and are then diagnosed with MAP. MAP occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH variants are associated with a cumulative CRC risk of about 80% by age 70, whereas monoallelic MUTYH variant-associated risk of CRC appears to be relatively minimal, although still under debate.[2] Thus, inheritance for high-risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (i.e., between 10-99) 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 variants, and screening for variants associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome.[3]

Lynch Syndrome

Patients with Lynch syndrome have a predisposition to CRC and other malignancies as a result of an inherited variant 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 variants for many of these patients and now includes some who are negative for MMR variants and likely have variants in as-yet unidentified genes. For purposes of clarity and analysis, the use of Lynch syndrome in place of HNPCC has been recommended in several recent editorials and publications.

Lynch syndrome is estimated to account for 3% to 5% of all CRC and is also associated with an increased risk of other cancers such as endometrial, ovarian, urinary tract, and biliary tract cancer. Lynch syndrome is associated with a risk of developing CRC by age 70 years of approximately 27% to 45% for men, and 22% to 38% for women, after correction for ascertainment bias.[4] 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 variants in one 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 variant in the MSH6 and PMS2 genes, although for most cancers still significantly higher than that of the general population.[3, 4] Estimated cumulative risks of any associated cancer for a carrier of a variant in any MMR gene do not begin to increase until after age 30 years.

Lynch syndrome variants are heterozygous; that is, only one of the two gene alleles contains a variant. In rare cases both alleles contain the variant (i.e., biallelic MMR gene variants). This unusual syndrome has been described in multiple families and is to a large extent the result of consanguinity.[5] Children with biallelic MMR variants may develop extracolonic cancers in childhood, such as brain tumors, leukemias, or lymphomas. Those unaffected or surviving early malignancies are at high risk of later CRC (average age of CRC diagnosis, 16.4 years[5]). 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 MUTYH-associated polyposis versus Lynch syndrome.

About 70% of Lynch syndrome patients have variants in either MLH1 or MSH2. Testing for MMR gene variants is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2 testing. Large gene sizes and the difficulty of detecting variants 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 variants. Available screening methods are MSI testing or 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.

Variants 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 (two to five 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.[6] Methodologic studies have also shown the importance of laser microdissection of the tumor tissue, comparison of tumor and normal cells, and a minimum proportion of tumor in relation to the quality of the test results. While the sensitivity of MSI testing is high, the specificity is low because approximately 10% of sporadic CRC are MSI-positive due to somatic hypermethylation of the MLH1 promoter. Additionally, some tumors positive for MSH6 variants are associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR variant testing.[7, 8]

Absent or reduced protein expression may be a consequence of an MMR gene variant. 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 variant, when sequencing is negative for a variant. In such cases, variants may be in unknown regulatory elements and cannot be detected by sequencing of the protein coding regions. Thus IHC may add additional information.

The BRAF gene is often mutated in CRC; when a particular BRAF variant (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present; to date no MLH1 gene variants have been reported.[9] Therefore, patients negative for MLH1 protein expression by IHC, and therefore potentially positive for an MLH1 variant, could first be screened for a BRAF variant. 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.[10]

Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR variants, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria[11] (low sensitivity but high specificity) and the Bethesda guidelines[6] (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 variant; family members would be tested only for the family variant; 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 variant.

Recently, novel deletions have been reported to affect the expression of the MSH2 MMR gene in the absence of a MSH2 gene variant, 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 variant is found by sequencing.

Distinct from patients with EPCAM deletions, rare Lynch syndrome patients have been reported without detectable germline MMR variants although IHC testing demonstrates a loss of expression of one of the MMR proteins. In at least some of these cases, research has identified germline "epimutations," i.e., methylation of promoter regions that control the expression of the MMR genes.[12-14] Such methylation may be isolated or in conjunction with a linked genetic alteration near the affected MMR gene. The germline epimutations may arise de novo or may be heritable in either Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic 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 be helpful 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 variants MLH1, MSH2, MSH6, and 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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of Clinical Laboratory Improvement Act (CLIA). Genetic tests reviewed in this protocol are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration does not require regulatory review of these tests.

Related Protocols

Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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