Lynch Syndrome/Hereditary Nonpolyposis Colorectal Cancer

Colorectal cancer (CRC) exhibits the characteristics of familial clustering in ~10-15% of cases. The most common cause of hereditary CRC is Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC). LS is caused by a germline mutation in one of the genes within the DNA mismatch repair (MMR) system.

Indications for Ordering

Microsatellite instability (MSI) and/or immunohistochemistry (IHC) tumor analyses

- Universal screening for LS in all individuals with newly diagnosed CRC
- Universal screening for LS in individuals with endometrial cancer
- Germline MMR gene testing
- Order following abnormal screening test result
- Confirms diagnosis of LS

Disease Overview

Incidence

- Accounts for 2-4% of CRC and ~1-2% of endometrial cancers
- Most common hereditary CRC syndrome
- Most common cause of hereditary endometrial cancer

Risk Estimates

The following lifetime risk estimates apply to individuals with MLH1 and MSH2 pathogenic variants; risks for variants in MSH6 or PMS2 may be lower

- CRC – 52-82%
- Endometrial – 25-60%
- Prostate – ~30%
- Ovarian – 11-24%
- Gastric – 6-13%
- Hepatobiliary tract – 1-4%
- Urinary tract – 1-7%
- Small bowel – 3-6%
- Brain/central nervous system – 1-3%
- Sebaceous neoplasms – 1-9%
- Pancreatic – 1-6% (MLH1 and MSH2 only)

Tests to Consider

Screening Studies (Requires Pathological Tissue)

Mismatch Repair by Immunohistochemistry 0049302
Method: Qualitative Immunohistochemistry

- First-line screening test for newly diagnosed CRC, endometrial carcinoma, and LS
- Highly recommended prior to ordering germline MMR gene testing
  - Directs subsequent genetic diagnostic testing
- Testing for CRC and other solid tumors to qualify patients for certain immune checkpoint inhibitor treatment

Mismatch Repair by Immunohistochemistry with Reflex to BRAF Codon 600 Mutation and MLH1 Promoter Methylation 2002327
Method: Qualitative Immunohistochemistry/Qualitative Real-time Polymerase Chain Reaction

- Screening for HNPCC/LS (NCCN, Colorectal, 2018)
If MLH1 IHC is abnormal, evaluations of BRAF codon 600 and, possibly, MLH1 methylation are performed. Definitive diagnosis of LS requires additional targeted MMR germline molecular studies. Do not use in endometrial cancer.

Recommended reflex test to differentiate between LS and sporadic CRC in tumors showing loss of MLH1. If no BRAF variant is detected, MLH1 promoter methylation is evaluated.

Reflex screening test for LS in non-CRC tumors (e.g., endometrial carcinoma). If MLH1 expression is lost, MLH1 methylation is performed.

Mismatch Repair by Immunohistochemistry with Reflex to MLH1 Promoter Methylation 2005270
Method: Qualitative Immunohistochemistry/Qualitative Real-time Polymerase Chain Reaction

Recommended test to distinguish between LS and sporadic non-CRC tumors with loss of MLH1.

Diagnostic Germline Genetic Studies

Specimen – peripheral blood

Germline genetic testing is available for all 4 MMR genes known to cause LS, either separately or as part of the hereditary gastrointestinal (GI) cancer panel (see Related Tests).

HNPCC/Lynch Syndrome (MLH1) Sequencing and
Detect germline MLH1 variants

Use in MMR-deficient carcinoma with suggestive IHC results (loss of MLH1 and PMS2 proteins), negative for the BRAF codon 600 pathogenic variant, and with normal MLH1 promoter methylation studies

Detect germline MSH2 variants

Use in MMR-deficient carcinoma with suggestive IHC results (loss of MSH2 and MSH6 proteins)

Includes evaluation of EPCAM exon 9 deletions and 10 Mb inversion of MSH2 exons 1-7

Detect germline MSH6 variants

Use in MMR-deficient carcinoma with suggestive IHC results (isolated loss of MSH6 protein)

Detect germline PMS2 variants

Use in MMR-deficient carcinoma with suggestive IHC results (isolated loss of PMS2 protein)

Order if sequencing studies have been performed previously at

Consider MLH1 methylation ± BRAF V600E studies

If methylation and BRAF studies are negative, follow with MLH1 germline genetic testing

Absence of PMS2 only

PMS2 germline pathogenic variant likely

Consider PMS2 germline testing

If PMS2 testing does not identify a germline pathogenic variant, consider MLH1 germline testing

Absence of both MSH2 and MSH6

MSH2 germline pathogenic variant likely

Consider MSH2 germline testing

Absence of MSH6 only

MSH6 germline pathogenic variant likely

Consider MSH6 germline testing

If MSH6 testing does not identify a germline pathogenic variant, consider MSH2 germline testing

• Limitations
  
  o ~10% of individuals with LS will have IHC tests that show normal staining of the MMR proteins
  
  o Because the correlation of MSI with IHC is not 100%, direct testing of MSI by PCR may be helpful
  
  o Screens for LS only and does not evaluate other hereditary causes of CRC or endometrial cancer

BRAF Codon 600 Mutation Detection with Reflex to MLH1 Promoter Methylation

• Analytical sensitivity
  
  o Methylation levels >10% are reported as positive

• Results
  
  o BRAF V600E detected
    
    ■ Presence in MMR-deficient CRC indicates the tumor is probably sporadic and not associated with LS
    
    ■ Further germline testing not typically indicated
  
  o MLH1 promoter methylation detected
    
    ■ Presence in an MSI CRC indicates the tumor is probably sporadic and not associated with LS
    
    ■ Further germline testing not typically indicated
  
  o No variants detected
    
    ■ In MSI-H tumors with loss of MLH1 protein by IHC, MLH1 germline testing indicated

Germline Genetic Studies (MLH1, MSH2, MSH6, PMS2, or EPCAM)

• Sensitivity/specificity
  
  o Proportion of LS attributed to pathogenic variants in specific MMR gene
    
    ■ MLH1 – 50%
    
    ■ MSH2 – 40%
- **MSH6** – 7-10% \(^{5,6,7}\)
- **PMS2** – <5% \(^{8}\)
- **EPCAM** – ~1-3% \(^{9}\)

- Analytical sensitivity/specificity – 99%

- **Results**
  - Positive – 1 pathogenic variant detected
    - Predicted to be causative for LS
  - Negative – no pathogenic variants detected
    - Diagnosis of LS unlikely, but not excluded
  - Inconclusive – variant detected, but whether it is benign or pathogenic is unknown

- **Limitations**
  - Not evaluated
  - Regulatory region and deep intronic variants
  - Sequence variants and large deletion/duplications in genes other than MLH1, MSH2, MSH6, and PMS2
  - Sequence variants in EPCAM
  - Large deletions/duplications in EPCAM, other than exon 9
  - Large gene inversions, other than the MSH2 10 Mb exons 1-7 inversion
  - Causes of hereditary CRC or endometrial cancer other than LS
  - Diagnostic errors can occur due to rare sequence variations

- **References**


Related Information

Colorectal Cancer
Lynch Syndrome - Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
Lynch Syndrome (HNPCC) Testing Algorithm

Related Tests

Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication 2013449

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray/Sequencing/Multiplex Ligation-dependent Probe Amplification
