Lynch Syndrome (HNPCC) Testing

**Abbreviations**
- HNPCC: Hereditary nonpolyposis colorectal cancer
- IHC: Immunohistochemistry
- PCR: Polymerase chain reaction

**All colorectal cancer and endometrial tumors**

Screen for mismatch repair deficiency by IHC

**Normal per IHC**

- High clinical suspicion of Lynch syndrome
  - Yes: ORDER Microsatellite instability testing
  - No: No additional testing

**Abnormal per IHC**

- Abnormal staining for MLH1\(^a\) and PMS2
  - Abnormal staining for MSH2 and MSH6
    - Associated with germline pathogenic variants in MSH2 or, more rarely, MSH6
      - **CONSIDER** Genetic panel testing OR MLH2 testing followed by MSH6 testing if negative
    - Abnormal staining for MSH6
      - Associated with germline pathogenic variants in MSH6 or, more rarely, MSH2
        - **CONSIDER** Genetic panel testing OR MLH6 testing followed by MSH2 testing if negative
  - Abnormal staining for PMS2
    - Associated with germline pathogenic variants in PMS2 or, more rarely, in MLH1
      - **CONSIDER** Genetic panel testing OR PMS2 testing followed by MLH1 testing if negative

**Instability in at least 2 of 5 microsatellite markers**

- Instability in 1 microsatellite marker
  - High clinical suspicion of Lynch syndrome
  - **ORDER** Microsatellite instability testing
  - Consider germline testing of mismatch repair genes

**Instability in 1 microsatellite marker**

- No instability present
  - Variant present
    - Test for *BRAF* V600E variant
  - Variant absent (wild type)
    - Associated with germline pathogenic variants in MLH1 or, more rarely, in PMS2
      - **CONSIDER** Genetic panel testing OR MLH1 testing followed by PMS2 testing if negative

**No instability present**

- Probable sporadic colorectal cancer
  - Lynch syndrome unlikely

**Loss of MLH1** may be due to either acquired hypermethylation (in sporadic tumors) or a germline mutation (in Lynch syndrome).

\(^a\)Panel (reflex) tests are available (Mismatch Repair by Immunohistochemistry with Reflex to *BRAF* Codon 600 Mutation and MLH1 Promoter Methylation; Mismatch Repair by Immunohistochemistry with Reflex to MLH1 Promoter Methylation).

\(^a\)Not applicable to endometrial cancers; order only MLH1 Promoter Methylation.

\(^a\)Consider targeted testing if a specific variant has been previously identified in a family member.