Mismatch Repair (MMR) Analysis by Immunohistochemistry

Effective Date: August 1, 2014
Performing Department: Molecular Pathology

Clinical Significance: Lynch syndrome, also referred to as hereditary non-polyposis colorectal cancer (HNPPCC), is an inherited condition which increases an individual’s lifetime risk for colon cancer and several other tumors, including carcinoma of the endometrium, ovary, stomach, pancreaticobiliary tract, proximal urothelial system, small bowel, and some primary brain tumors (typically glioblastoma). In the skin, there also is an increased risk for sebaceous neoplasia and keratoacanthomas, a condition known as Muir-Torre syndrome. The inheritance pattern is autosomal dominant. Lynch syndrome is the most common heritable colon cancer syndrome, accounting for 3-5% of colon cancers. These patients show loss-of-function defects in the DNA mismatch repair (MMR) system, which manifests as high levels of microsatellite instability and accumulation of genetic error in tumor tissue.

This test will detect most, but not all Lynch syndrome patients. However, detection approaches 100% when this test is combined with a second test modality such as microsatellite instability (MSI) by PCR. Additionally, the presence of BRAF V600E mutation in tumor tissue essentially excludes the possibility of Lynch syndrome.

Method: The genes controlling the Mismatch Repair system are MLH1, PMS2, MSH2, and MSH6. These code for protein heterodimers in the multimeric MMR protein complexes that correct DNA strand alignment and base matching errors during DNA replication. When the genes are nonfunctional, the proteins are not expressed. This is identified by immunohistochemistry in sections of tumor tissue that are reviewed and interpreted by a pathologist.

Use: This test is a screening tool to identify patients at risk for Lynch syndrome, and may help target a mutated gene for confirmatory DNA sequencing or direct other molecular testing in the context of genetic counseling. Additionally, results of this test may be used to guide 5-fluorouracil (5-FU) treatment decisions in selected patients with colorectal adenocarcinoma.

Reference Range: Immunohistochemistry (IHC) slides for each MMR gene are determined to have either intact nuclear expression of MMR proteins in >50% of tumor cells, or loss of nuclear expression of MMR proteins in ≤ 5% of tumor cells. An interpretation of results is included for all cases.

Specimen Requirements and Collection:
• Submit formalin fixed, paraffin embedded tissue block. Neutral buffered formalin is the preferred fixative and tissue should be sectioned and fixed as soon as possible after surgery for best immunohistochemical staining properties. In selecting the paraffin block, submit the largest area of tumor available that shows the least degeneration or necrosis and the least fibrous stroma. Preservation of nuclear detail can help assess quality of fixation
• Tissue block should show at least 20% nucleated tumor cells and some background normal tissue
Two separate tissue blocks, one with normal tissue and one showing tumor, are required if MSI PCR testing is also requested
• Small biopsy or cytology cell block may be acceptable depending on the amount of tumor present.
• Please include copy of corresponding pathology or cytology report

**Cause for Specimen Rejection:**
• Insufficient well preserved tumor cells present in submitted tissue block when assessed by routine light microscopy
• Specimens submitted with non-representative tissue type
• Frozen specimens
• Specimens processed in alternative fixatives (alcohol, Prefer®,) or heavy metal fixatives (B-4 or B-5)

**Specimen Storage and Transportation:** Room temperature. Avoid excessive heat (greater than 55°C). Transport in cooled container during summer months.

**Specimen Stability:** Room temperature: Indefinitely; Refrigerated: Indefinitely; Frozen: Unacceptable

**Testing Schedule:** Once per week.

**Estimated Turnaround Time:** 7 days

**Order:** Mismatch Repair (MMR) Analysis by Immunohistochemistry (IHC).
Test # 38520  CPT: 88342 x 4

**Other Related Tests:**
Colorectal Carcinoma (CRC) Mutation Analysis (Identifies mutations in BRAF, KRAS, and NRAS).
Test # 36268; CPT: 81210, 81275, 81479. CRC specimens are also assessed for microsatellite instability. Mismatch Repair (MMR) by IHC (Test # 38520; CPT: 88342x4) and, when appropriate, Microsatellite Instability (MSI) by PCR (Test # 38547; CPT: 81301) will be added and reported separately. Additional charges apply.

- **Microsatellite Instability by PCR.**
  Test # 38547  CPT: 81301*

- **KRAS mutation analysis**
  Test # 36272  CPT: 81275*

- **NRAS mutation analysis**
  Test # 36274  CPT: 81479*

- **BRAF mutation analysis**
  Test # 36273  CPT: 81210*

**Solid Tumor Mutation Analysis (Identifies mutations in BRAF, KRAS, NRAS, EGFR and KIT).**
Test # 36271,  CPT: 81275, 81235, 81210, 81479 x 2*

*Note: Tissue based tests will include CPT 88381 when manual microdissection is required.

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