Microsatellite Instability Testing in Colon and Endometrial Cancer

Microsatellite instability (MSI) is used to help identify patients with Lynch syndrome. In colorectal cancer patients, MSI-high status is associated with a better prognosis and with non-response to 5-FU.

**Biology and Clinical Utility:** One in 35 colorectal adenocarcinoma patients, and one in 42 endometrial adenocarcinoma patients have Lynch syndrome which increases the likelihood of developing certain malignancies (gastric, small bowel, ovarian, pancreatic, urinary and biliary tracts, brain, sebaceous gland carcinomas, and keratoacanthoma). To identify these patients, all newly diagnosed colorectal or endometrial cancers are first tested for MSI-high status. MSI-high status is due to germline (heritable) or somatic inactivation of a DNA mismatch repair gene (e.g. MLH1, MSH2, MSH6, PMS2), which in turn reduces capacity to correct errors during DNA replication. This DNA repair defect is associated with widespread genomic hypermutation and with small insertions or deletions of repeat units in microsatellite sequences. Any patient with an MSI-high tumor is further evaluated for Lynch syndrome and, once diagnosed, the patient and blood relatives are counseled about strategies for early cancer detection and risk reduction. On the other hand, MSI-high is also found in 12% of sporadic colorectal carcinomas harboring an acquired (not inherited) defect in mismatch repair --typically methylation-related silencing of MLH1. MSI-high colorectal cancer has a better prognosis, and affected patients do not tend to benefit from treatment with 5-fluorouracil (5FU)-containing regimens.

**Clinical Indications for MSI testing:**
1. Newly diagnosed colorectal or endometrial adenocarcinoma as part of an algorithm to identify Lynch syndrome.
2. For prognosis and for 5FU drug responsiveness in colorectal adenocarcinoma.

**Laboratory Testing for Microsatellite Instability:** The assay is performed on colorectal or endometrial carcinoma tissue and matched non-malignant tissue. The preferred specimen is ten unstained paraffin sections (10uM thick, plain glass), plus an H&E-stained slide on which areas with >70% malignant cells are circled. In addition, submit blood (3mL, EDTA) or ten unstained paraffin sections of any non-tumor tissue plus an H&E-stain. Tumor is enriched by macrodissection, and DNA is PCR-amplified (Promega) across five mononucleotide microsatellites (BAT-25, BAT-26, NR-21, NR-24, MONO-27) and sized by capillary electrophoresis. Allelic profiles of tumor and non-tumor samples are interpreted by a pathologist in concert with clinicopathologic findings. MSI-high signifies instability in two or more microsatellites, MSI-low or MSI-stable signifies no clinically significant instability.

**References:**

**To consult a pathologist** about indications for testing or the significance of a result, call the Molecular Genetics Lab at (984) 974-1825 or Dr. Gulley at (919) 843-4595. Email: margaret_gulley@med.unc.edu


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