

Microsatellite Instability Testing in Colon Cancer

The UNC Hospitals Molecular Genetics Laboratory offers a polymerase chain reaction (PCR) assay for detecting microsatellite instability (MSI) in patients with suspected Hereditary Non-Polyposis Colorectal Carcinoma (HNPCC, or Lynch Syndrome). MSI analysis is performed on fixed, paraffin-embedded tissue representing the colonic adenocarcinoma, and on benign tissue that is usually available from the same surgical procedure.

Biology and Clinical Utility of Microsatellite Instability:

Microsatellite instability is detected in 90% of colon cancers arising in patients with HNPCC, and in 10-15% of sporadic colorectal carcinomas. The MSI phenotype is associated with germline or somatic inactivation of a DNA mismatch repair gene (MLH1, MSH2, MSH6, or PMS2). Inactivation of these genes results in an inability to correct small insertions or deletions of repeating units in microsatellite sequences during DNA replication. Patients with microsatellite instability – high (MSI-H) tumors are at elevated risk of carrying a heritable (germline) mutation in a mismatch-repair gene; however, the majority of MSI-H patients have a sporadic rather than inherited form of cancer.

Clinical Indications for Testing:

1. Colorectal cancer diagnosed in a patient younger than 50 years of age.
2. Colorectal cancer in a patient with synchronous or metachronous HNPCC-associated tumors*, regardless of age.
3. Colorectal cancer with Crohn-like infiltrating lymphocytes, mucinous or signet ring type, medullary or poorly differentiated, in a patient younger than 60 years of age.
4. Colorectal cancer in a patient whose first-degree relative has an HNPCC-associated tumor diagnosed at younger than age 50 years.
5. Colorectal cancer in a patient who has two or more first- or second- degree relatives with an HNPCC-associated tumor, regardless of age.

* HNPCC-associated tumors include colorectal, endometrial, gastric, small bowel, ovarian, pancreatic, urinary, and biliary tract tumors, brain, sebaceous gland, and keratoacanthoma.

Laboratory Testing for Microsatellite Instability: The MSI test is ordered by faxing a completed requisition form downloaded from our website. The Molecular Genetics Laboratory will then retrieve the patient's samples (normal and malignant paraffin-embedded tissues from a colectomy procedure) from Surgical Pathology. Therefore, testing is available only on colon cancer patients whose tissue blocks are available for testing. DNA is isolated from normal and cancer tissue and then PCR-amplified across five mononucleotide microsatellites (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) and analyzed by fluorescent capillary electrophoresis (Promega). Allelic profiles from the normal and malignant tissue are compared to determine the MSI status which is reported as microsatellite instability high (MSI-H) which is considered abnormal, or microsatellite instability low (MSI-L) or microsatellite stable (MSS) which are considered normal results. Genetic counseling is recommended for patients with MSI-H results; call the Cancer Genetics Clinic at (919) 843-8724 for counseling and related patient services.

References:

1. Umar A, Boland CR, Terdiman JP. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch Syndrome) and microsatellite instability. *J Nat Can Inst* 2004 96;261-268.
2. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer). *NEJM* 2005; 352:1851-1860.

Questions? Call the UNC Molecular Genetics Lab at (984) 974-1825 or email Dr. Karen Weck at Karen.Weck@unchealth.unc.edu

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