Microsatellite Instability Testing in Colon and Endometrial Cancer

The UNC Hospitals Molecular Genetics Laboratory offers a polymerase chain reaction (PCR) to detect microsatellite instability (MSI) in patients with suspected Lynch syndrome (e.g. Hereditary Non-Polyposis Colorectal Carcinoma, HNPCC). The assay is performed on fixed, paraffin-embedded tissue representing colon adenocarcinoma or endometrial adenocarcinoma.

Biology and Clinical Utility: About one in 35 colorectal carcinoma patients, and about one in 42 endometrial cancer patients have Lynch syndrome. Microsatellite instability is detected in 90% of colon cancers arising in patients with Lynch Syndrome, and also in 10-15% of sporadic colorectal carcinomas. MSI is also found the vast majority of endometrial adenocarcinomas arising in Lynch syndrome. The MSI phenotype is associated with germline or somatic inactivation of a DNA mismatch repair gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), which in turn causes inability to correct small insertions or deletions of repeated units in microsatellite sequences during DNA replication. A patient with a microsatellite instability-high (MSI-H) tumor may be further tested for heritable (germline) mutation in a mismatch-repair gene and, if found, the patient and blood relatives may be counseled about strategies for early cancer detection and risk reduction. On the other hand, the majority of MSI-H tumors will be identified as sporadic by further testing, which greatly reduces the likelihood of developing new malignancies.

Clinical Indications for Testing:

1. Colorectal cancer or endometrial adenocarcinoma diagnosed in a patient <50 years of age.
2. Colorectal cancer in a patient with synchronous or metachronous Lynch syndrome-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 a Lynch syndrome-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 a Lynch syndrome-associated tumor, regardless of age.

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

Laboratory Testing for Microsatellite Instability: The MSI test is ordered by faxing a completed requisition form (downloaded from our Lab's website+). The Molecular Genetics Laboratory will retrieve the patient's samples (normal and malignant paraffin-embedded tissues from a colon or endometrial resection/biopsy procedure) from Surgical Pathology archives. DNA isolated from normal and cancer tissue is 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, an abnormal result), or microsatellite instability low or stable (MSI-L or MSS, both normal results). Genetic counseling is recommended for patients with MSI-H results; call the Cancer Genetics Clinic at (919) 843-8724 for counseling services.

References:

1. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer). NEJM 2005; 352:1851-1860.
2. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 11:42-65, 2009.
3. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control 16:14-22, 2009.

Questions? Call the Molecular Genetics Lab at (919) 966-4408

+Website: http://labs.unchealthcare.org/directory/molecular_pathology/index_html