Microsatellite Instability Test in Tumor Tissue

Microsatellite instability (MSI) status helps identify patients with Lynch syndrome, and it also identifies cancers that may respond better to immunotherapy or certain other interventions.

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 a range of malignancies (e.g. gastric, small bowel, ovarian, pancreatic, urinary and biliary tracts, brain, sebaceous gland carcinomas, and keratoacanthoma). Practice guidelines recommend that all newly diagnosed colorectal or endometrial carcinomas be tested for MSI-high status, which when present must be further evaluated to assess germline (*heritable*) *versus* somatic (*acquired*) inactivation of a DNA mismatch repair gene (e.g. *MLH1*, *MSH2*, *MSH6*, *PMS2*). Such inactivation reduces capacity to correct errors during DNA replication, which can lead to hypermutation including small insertions or deletions of repeat units in microsatellite sequences.

A *heritable* defect in mismatch repair defines Lynch syndrome and, once diagnosed, the patient and blood relatives should be counseled about strategies for early cancer detection and risk reduction. On the other hand, MSI-high status characterizes 12% of sporadic colorectal carcinomas due to an *acquired* (not *inherited*) defect in mismatch repair --typically methylation-related silencing of *MLH1*. Thus, when MSI-high status is detected in a colon or endometrial adenocarcinoma, our testing lab may reflexively evaluate for *MLH1* methylation to help assess likelihood of Lynch syndrome, particularly if *MLH1* protein expression is diminished in the malignant cells.

Regardless of whether a cancer has a *heritable* or *somatic* mechanism for mismatch repair deficiency, such tumors oftern have a better prognosis and are more likely to respond to certain immunotherapy regimens, in part because tumor-related neoantigens that accumulate might trigger immune-mediated cell killing. Finally, MSI-high colorectal cancer patients do not tend to benefit from treatment with 5-fluorouracil (5FU)-containing regimens.

Clinical Indications for MSI testing:

1. Newly diagnosed cancer as part of an algorithm to identify Lynch syndrome.
2. Predict response to immunotherapy among patients hving a cancer type commonly associated with MSI-high status.
3. For prognosis and for 5FU drug responsiveness in colorectal adenocarcinoma.

Laboratory Testing for Microsatellite Instability: The assay is performed on cancer 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 >50% malignant cells are circled. In addition, submit any non-tumor tissue such as blood (3mL, EDTA) or ten unstained paraffin sections plus an H&E slide. After macrodissection, DNA is PCR-amplified (Promega) across five mononucleotide microsatellites (BAT-25, BAT-26, NR-21, NR-24, MONO-27) and sized by capillary electrophoresis to evaluate for instability in two or more microsatellites defining MSI-high status. Allelic profiles are interpreted by a pathologist in concert with clinicopathologic findings.

References:

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: multiple guidelines including 'Colorectal Cancer Screening' and 'Genetic/Familial High-Risk Assessment: Colorectal', www.nccn.org
2. Li K, Luo H, Huang L, Luo H, Zhu X. Microsatellite instability: a review of what the oncologist should know. Cancer Cell Int. 2020 20:16. PMCID: PMC6958913.

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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