

# FOCUS ON THE WAR AGAINST CANCER

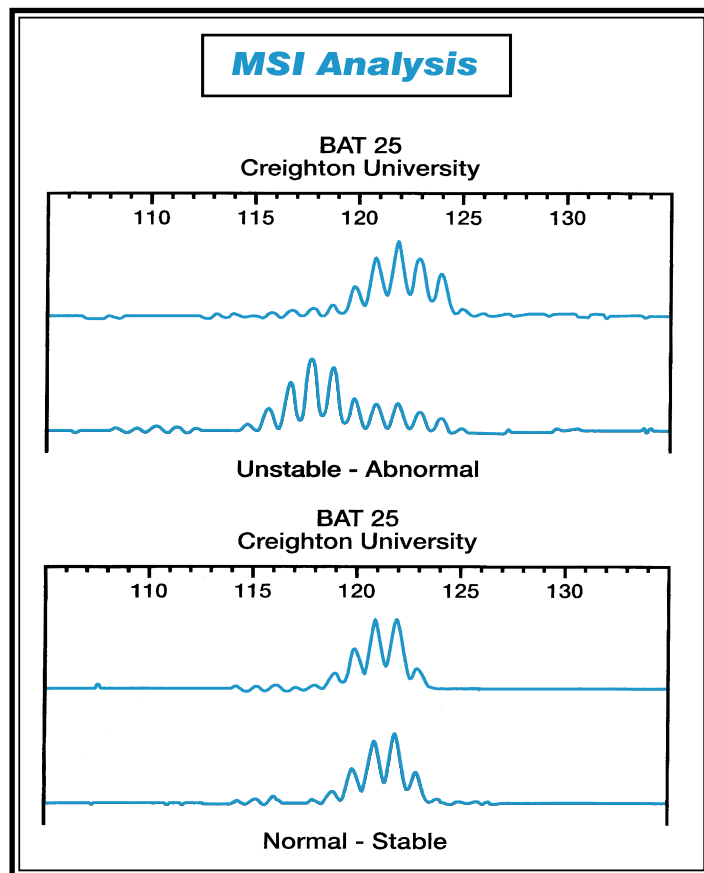
## Microsatellite Instability (MSI) Analysis for Colorectal Cancer

Cancer of the large intestine is the fourth most common type of human cancer and the third leading cause of cancer deaths in the United States. Frequently, (in about 10-12% of colon cancer patients) the disease appears in more than one family member or in more than one generation. This is known as hereditary colon cancer and one variant of this familial clustering is known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch Syndrome. The disease is named after Creighton University oncologist Dr. Henry Lynch. However, not all familial occurrences of cancer are examples of HNPCC. Patients who are diagnosed with colon cancer at a relatively young age (around or before 50 years of age) and have first degree relatives with colon cancer are the most likely to have HNPCC. There are four defined criteria for describing potential HNPCC patients. These criteria are as follows: (1) colorectal cancer (CRC) diagnosed before the age of 50 years; (2) a second CRC; (3) CRC and another cancer arising in different organs (endometrium, ovary, stomach, liver, small bowel, or carcinoma of the renal pelvis or ureter); or (4) a polyp arising in large bowel (colorectal adenoma) that on pathologic examination showed high grade dysplasia and was diagnosed in a patient before the age of 40 years. These types of familial colon carcinoma are caused by mutations in genes called the mismatch repair genes and mutations found in these genes are specific for each affected HNPCC family.

The first diagnostic step for patients with medical histories suggestive of HNPCC is the test for microsatellite instability (MSI) on a sample of the colon tumor tissue itself. In this test pathologists look for alterations in the repeated sequences of tumor DNA termed microsatellites, which are short repetitive sequences of human DNA. In the patients with mutations in mismatch repair genes this test will be positive. However, a positive MSI test must be confirmed by full mutation analysis of the genes known to cause HNPCC. This step requires that the patient and their family agree to genetic counseling prior to testing.

Pathologists have other tests available for detection of HNPCC. For example, immunohistochemical staining for the mismatch repair proteins, that is used in conjunction with the MSI testing helps determine which of the genes has been mutated thus causing the disease. These two tests used in concert can provide a focus for final diagnosis of HNPCC.

Testing for tumor microsatellite instability may have additional benefits for the patients that do not have a hereditary form of colon cancer. In a recent report in *The New England Journal of Medicine*, MSI status was correlated with the efficacy of adjuvant chemotherapy with fluorouracil (a standard drug given to most colon cancer patients). Patients with tumors that were MSI positive, showed no benefit with fluorouracil treatment. Thus, MSI testing appears to be useful for predicting the efficacy of adjuvant



The figure represents a plot of one of the five HNPCC MSI markers for both an MSI stable and an MSI unstable situation with the comparison of normal versus cancer DNA from each patient.

chemotherapy with fluorouracil in colon cancer. This initial study is being repeated with larger patient numbers and different patient populations to determine the overall significance of this initial study.

The MSI testing is a PCR based assay that is used to amplify 5 DNA mononucleotide microsatellite markers known to be associated with HNPCC. Fragment size analysis is performed for each marker comparing tumor tissue DNA to normal tissue DNA. The difference in the size of the fragments generated from the two tissue types from the same patient is the basis for instability analysis. This technique has been shown to have a sensitivity of 98.5% for the detection of each marker tested. The test requires a fresh sample of the tumor or a paraffin block, and a peripheral blood specimen from the patient.



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