

HNPCC/ Lynch Syndrome, Microsatellite Instability by PCR

*TO DETERMINE IF A TUMOR IS LIKELY CAUSED BY A
GERMLINE HEREDITARY NON-POLYPOSIS COLON CANCER
(HNPCC) MUTATION*

Disease Overview

- Microsatellites (short nucleotide sequence repeats dispersed throughout the genome) have an increased risk for expansion or contraction during DNA replication. In tumors with mismatch repair deficiency, these expansions or contractions are not repaired, leading to the phenomenon of microsatellite instability (MSI). MSI testing of colorectal or other HNPCC-associated cancers is the first step in the evaluation of an individual or family suspected of having HNPCC.
- The lack of MSI in colorectal or other HNPCC-associated cancers decreases, but does not exclude, the risk of HNPCC. Stable tumors have been identified in individuals with germline mutations in *MSH6*, a rare cause of HNPCC.
- Both inherited and sporadic tumors with MSI are reportedly associated with a better prognosis than stable colon cancers.
- Fluorouracil-based adjuvant chemotherapy appears to be effective only in individuals with microsatellite stable colon cancers and may be harmful to those with unstable cancers.

Epidemiology

- Approximately 90 percent of HNPCC-associated colorectal cancers show MSI. The frequency of MSI in non-colorectal HNPCC-associated cancers is unknown.
- MSI may also be seen in approximately 15 percent of sporadic colorectal cancers due to acquired hypermethylation of the *MLH1* promoter.
- Of all endometrial cancers, approximately 20 percent show MSI and 2 percent have a detectable mismatch repair gene mutation.

Genetics

- Autosomal dominant with reduced penetrance.
- HNPCC is actually recessive at the cellular level, requiring a second mutation to occur in the corresponding normal mismatch repair gene on the opposite allele.
- Deleterious mutations in any one of four different mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) causes HNPCC.
- Ninety percent of identified HNPCC mutations are detected in *MLH1* and *MSH2*.

Indications for Ordering

- To assess the probability of a germline mismatch repair gene mutation in an individual with colorectal or another HNPCC-associated cancer.
- For prognostic information in individuals with colon cancer.
- To aid in the clinical decision of whether or not to provide adjuvant chemotherapy.

Additional Ordering Notes

- Normal tissue is used as a comparison to determine MSI instability. If normal tissue is not included in the tumor block, a peripheral blood sample may be obtained for this purpose.
- A testing algorithm for HNPCC is available at:
<http://www.arupconsult.com/Algorithms/HereditaryColorectalCancer.pdf>

Interpretation

- MSI High indicates a tumor with instability in two or more mononucleotide microsatellite repeats. MSI High occurs in approximately 90 percent of colorectal cancers from individuals with HNPCC and in 10–15 percent of sporadic colon cancer. IHC staining (ARUP test# [0049302](#)) for mismatch repair gene proteins should be performed to determine the specific mismatch repair gene that should be targeted for mutation testing.
- MSI Indeterminate indicates a tumor with instability in one of five mononucleotide microsatellite repeats. Since instability in even a single mononucleotide marker can be indicative of a mismatch repair deficient tumor, it is recommended that such results be analyzed in concert with IHC staining for mismatch repair genes (ARUP test# [0049302](#)).
- MSI Stable indicates a lack of microsatellite instability in a tumor. This is unusual in colorectal cancers from individuals with HNPCC, although it does not completely exclude this possibility. IHC staining for mismatch repair genes (ARUP test #[0049302](#)) may be helpful in eliminating this possibility. Lack of microsatellite instability does not rule out the possibility of other hereditary cancer syndromes.

Limitations

- Tumors from individuals with *MSH6* mutations may not exhibit microsatellite instability by PCR; evaluation of these individuals by immunohistochemistry may be helpful.
- Non-colorectal HNPCC-associated cancers or cancer precursors (colon adenomas) may not exhibit similar degrees of instability and may therefore lead to false negative MSI results.

Methodology

DNA from normal and tumor tissue is amplified by PCR for five microsatellite markers: BAT-25, BAT-26, MONO-27, NR-21, and NR-24. Fluorescently labeled products are detected and sized by capillary electrophoresis. Patterns of normal and tumor genotypes are compared for each marker and scored as stable or unstable.

Related Tests

- Microsatellite Instability/HNPCC by Immunohistochemical Stain (0049302)
- BRAF V600E Mutation with Reflex to *MLH1* Promoter Methylation, Paraffin (0051750)
- HNPCC/Lynch Syndrome (*MLH1*) Sequencing and Deletion/Duplication (0051650)

- HNPCC/Lynch Syndrome (*MSH2*) Sequencing and Deletion/Duplication (0051654)
- HNPCC/Lynch Syndrome (*MSH6*) Sequencing and Deletion/Duplication (0051656)
- HNPCC/Lynch Syndrome (*PMS2*) Sequencing and Deletion/Duplication (0051737)
- HNPCC/Lynch Syndrome Deletion/Duplication (2001728)
- Family Mutation, Targeted Sequencing (2001961)

References

1. Boland CR, et al. A National Cancer Institute workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Research* 1998;58:5248–57.
2. Ribic CM, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003;349:247–57.
3. Samowitz WS, et al. Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. *Cancer Epidemiol, Biomarkers Prev* 2002; 10:917–23.
4. Samowitz WS, et al. The colon cancer burden of genetically defined hereditary nonpolyposis colon cancer. *Gastroenterology* 2001;121:830–8.

Test Information

0051740

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For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.