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CLINICAL UTILITY OF MICROSATELLITE INSTABILITY TESTING IN THE DIAGNOSIS AND MANAGEMENT OF HEREDITARY NON-POLYPOSIS COLON CANCER

AmeriPath, Inc. is pleased to announce the expansion of its molecular diagnostics program for Hereditary Non-polyposis Colon Cancer (HNPCC) testing with the availability of Microsatellite Instability (MSI) testing via Polymerase Chain Reaction (PCR).

Overview:

Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[1] is the most common form of hereditary colorectal cancer and accounts for about 3% of the total colorectal cancer cases.[2] This form of colorectal cancer and other Lynch-syndrome-associated cancers at different sites (e.g., stomach and endometrium) are characteristically associated with microsatellite DNA instability (MSI). Additionally, about 15% of patients with sporadic colorectal cancer also exhibit MSI.[3] Microsatellite DNA sequences are short, tandemly repeated sequences found throughout the genome. When the mismatch repair machinery is defective, gains and losses of microsatellite repeat units occur; this is known as microsatellite instability.

In Lynch syndrome, MSI results from mutation in one of several mismatch repair genes (MSH2, MLH1, MSH6, PMS2, or MLH3).[4] Tumors arise when the same mismatch repair gene that is mutated in the germ-line (an inherited mutation) is inactivated in the corresponding allele by a somatic (acquired) mutation. People with a germline defect in one of these mismatch repair genes have a lifetime risk of 85-90% of developing some kind of cancer.[4] These individuals benefit from increased screening and tailored surgical management.[2,4]

The MSI of sporadic colorectal cancer is usually attributed to hypermethylation of the promoter region of MLH1, which inhibits the expression of this mismatch repair gene.[5] Importantly, patients exhibiting MSI may have better survival from colorectal cancer than patients who lack MSI.[3,6] Some studies also suggest that colorectal cancer patients with MSI may not benefit from 5-fluorouracil-based chemotherapy.[7]

Clinical Utility of MSI Testing:

For patients diagnosed with colorectal cancer

- A high level of MSI indicates the need for further investigation and possible germline testing to detect defective mismatch repair genes.
- Patients exhibiting MSI have better prognosis than patients who lack MSI.[3,6]
- Several studies suggest that colorectal cancer patients with a high level of MSI may not benefit from 5-fluorouracil chemotherapy,[7] while they may benefit from other first line therapies, including irinotecan and oxaliplatin.[8]

For individuals with suspected Lynch Syndrome

- A high level of MSI indicates a need for germline testing of the affected individual. Subsequent identification of a mutation allows for predictive testing of at-risk relatives.

Revised Bethesda Guidelines[9]

According to the Revised Bethesda Guidelines, tumors from individuals should be tested for MSI in any of the following situations:

1. Colorectal cancer diagnosed in an individual younger than 50 years
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors (i.e., endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain tumors; sebaceous gland adenomas and keratoacanthomas; and carcinoma of the small bowel), in an individual regard-less of age
3. Colorectal cancer with MSI-high pathologic associated features diagnosed in an individual younger than 60 years
4. Colorectal cancer or an HNPCC-associated tumor diagnosed in at least one first-degree relative younger than 50 years
5. Colorectal cancer or HNPCC-associated tumor diagnosed at any age in two or more first-or second-degree relatives

Interpretation of Results:

Since MSI-positive colon tumors also occur in people without Lynch Syndrome, an MSI-positive tumor is not proof that Lynch Syndrome is present. Rarely, HNPCC patients do not exhibit MSI. Appropriate counseling should follow MSI testing so patients fully understand the residual risk associated with a negative result and the reproductive ramifications of a positive result.

AmeriPath now offers immunohistochemistry and MSI testing on either fresh tissue or paraffin-embedded tumor tissue by polymerase chain reaction (PCR) analysis. Mark Redston, M.D., AmeriPath's National Director of Molecular Diagnostics, is internationally known for his research on hereditary colon cancer and is actively investigating with Specialty Laboratories, AmeriPath's esoteric division, and the Molecular Profiling Institute the importance of Hereditary Non-polyposis Colon Cancer (HNPCC) testing, its impact on patient care and potential to save lives by identifying patients who can benefit from close follow-up and monitoring for recurrent or new malignancies. From these efforts AmeriPath will be able to educate physicians on new clinically relevant findings and provide easy access to new cutting-edge technologies.

For more information concerning AmeriPath Gastrointestinal Diagnostics Services call 1-866-840-7259, or visit AmeriPath's web site at www.ameripath.com.

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