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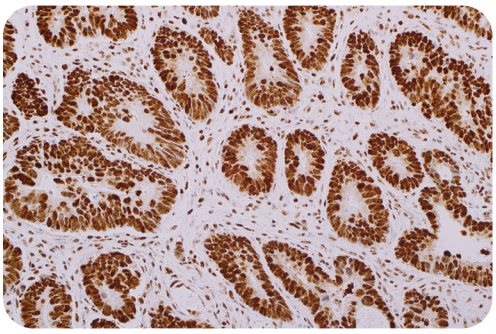
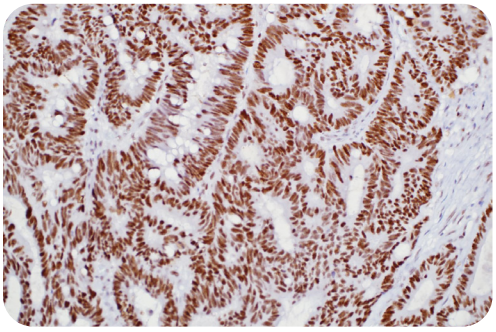
Lab & Production Materials

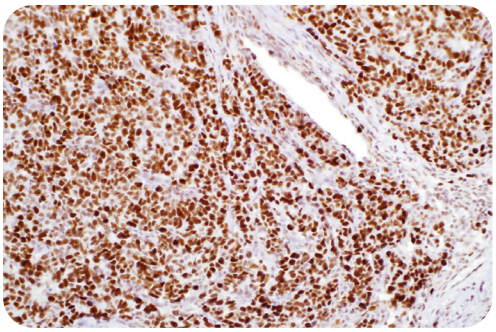
MERCK



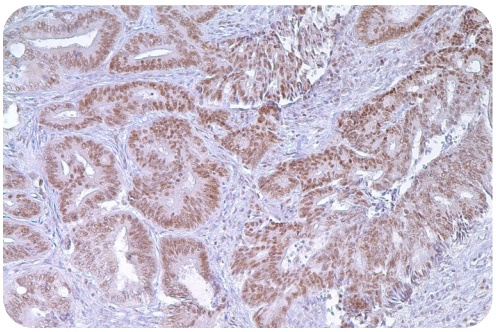
MLH1 (M1)



MSH2 (G219-1129)



MSH6 (SP93)



PMS2 (EPR3947)

Cell Marque™ Tissue Diagnostics

Microsatellite Instability, Mismatch Repair, and IHC

Microsatellite Instability

A microsatellite is a repeated sequence of DNA that ranges in length from one to six and in some instances up to ten nucleotides. During cell division, errors can occur in these DNA sequences. In normal, healthy cells, these errors are normally corrected through a natural repair mechanism within the cell.

Mismatch repair genes are responsible for correcting errors in the microsatellite sequence. The DNA of the dividing cells can become unstable due to the errors in the sequences when the mismatch repair genes do not function properly.[1] Defects in the mismatch repair genes lead to an accumulation of damaged cells, often known as dMMR. This term describes mismatch repair deficient genes. Over time, the damaged cells can lead to development of various cancers.

MSI-H is a term used to describe microsatellite instability "high", meaning there is significant instability in a tumor (30% or more of the microsatellite markers are unstable). MSI-H tumors are found in approximately 15% of colon tumors. Approximately ¼ of those tumors are associated with Lynch syndrome.

MSI-L indicates less than 30% of the microsatellite markers are unstable.

Microsatellite stable tumors (MSS) differ from MMR tumors since they have no demonstrable mutated microsatellite markers. MSS tumors account for 80-85% of colorectal tumors. They are often referred to as "cold tumors." Treatment differs for MSS versus MSI tumors.

Mismatch Repair Associated Syndromes

Lynch syndrome is an inherited autosomal dominant genetic condition. The affected mismatch genes are MLH1, MSH2, MSH6, PMS2 and EPCAM. Mutations of these genes modify the ability of the genes to repair microsatellite foci.

Studies have found that some but not all the mismatch repair genes are affected in Lynch syndrome cases.

This inherited condition predisposes patients to an increased risk of development of colorectal, urinary tract, pancreatic, liver and bile duct cancers. Women with Lynch syndrome have an increased risk of development of endometrial and ovarian cancers.[2]

Percentage of germline mutation deletion of mismatch repair proteins found in Lynch syndrome:

MLH1 - 40% | MSH2 – 35% | MSH6 – 10% | PMS2 - 5%

Muir-Torre syndrome (MTS) is a form of Lynch syndrome in which patients develop skin lesions. MLH1 or MSH2 are the affected genes in this rare genetic disease. It is characterized by sebaceous gland tumors that may precede or follow development of internal tumors. There is a significant incidence of colorectal cancer, with almost 50% of affected individuals developing this tumor type.[3,4]

Constitutional Mismatch Repair Deficiency Syndrome (CMMRD) is a rare genetic inherited condition with diagnosis by age seven. The affected mismatch genes include MLH1, MSH2, MSH6, PMS2 and EPCAM. PMS2 mutation is the most common cause of CMMRD syndrome.[5] The cancers associated with this syndrome include leukemia, glioblastoma, and colon cancer. Parents of individuals exhibiting this syndrome exhibit a high incidence of Lynch syndrome.

Depending on the source of the genetic mutation, a review of literature suggests a greater frequency of MLH1/MSH2 mutations in hematologic malignancies. Non-Hodgkin's lymphoma is the most common hematological disease associated with CMMRD.[6]

A greater prevalence of brain tumors has been found to be associated with mutations in MSH6 or PMS2.

Acquired/Sporadic Microsatellite Instability
This class of tumors is associated with nonhereditary MSI (non-Lynch syndrome). MSI is detected in approximately 15% of all colorectal cancers. Only 3% of those cancers are caused by Lynch syndrome. The remaining 12% are associated with a defect in the MLH1 gene.[3] These tumors are commonly found in the proximal colon. They commonly occur in individuals in their fifth and sixth decades.

Mismatch Repair and PD-L1 Expression

A publication by Willis, Sloan, Atkins, *et al.* reviewed expression of PD-L1 in ovarian cancer clear cell carcinomas and endometrial clear cell carcinomas with mismatch repair status. PD-L1 expression was found in 71% of cases (67% of ovarian and 75% of endometrial) with mismatch repair.[7]

Tissue Diagnosis of Mismatch Repair

Immunohistochemistry (IHC) and polymerase chain reaction (PCR) are widely accepted as appropriate testing methods for mismatch repair.

PCR testing utilizes a panel of microsatellite markers to demonstrate size shifts in loci. Detection of size shifts in 2 of 5 loci indicates a diagnosis of MSI-H.

IHC staining of biomarkers MLH1, MSH2, MSH6, and PMS2 is used to determine loss of expression in tumor specimens.[8] The criteria for classification of MSI-H/ dMMR using IHC is absence of staining (loss of expression) of one of the four biomarkers noted above.[9]

Timely and accurate testing and reporting is essential for diagnosis and appropriate of treatment.

MSI-H genetic mutation tumors often go undetected for lengthy periods of time.[10] Once diagnosed they are often treated with immunotherapy or a combination of chemo and immunotherapy, while colorectal MSS tumors are commonly treated with chemotherapy.

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For ordering information, please contact your local sales representative or distributor.

Intended Use: These products herein are intended for laboratory use in the detection of their respective proteins in formalin-fixed, paraffin-embedded tissue stained in qualitative immunohistochemistry (IHC) testing. These products are not a stand-alone diagnostic, and cannot be used for diagnosis, treatment, prevention, or mitigation of disease.

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