Medgenome Labs Ltd
Sy No 94/1C and 94/2, Tower-1, Veerasandra Village,
Attibele Hobli, Electronic City, Phase-1, Bangalore,
Karnataka, 560100.

MMR by Immunohistochemistry - Test Report

Patient Name	S A Shiranee M F Senevirathne	Order ID	1042163
Age / Gender	76 Years / Female	Sample ID	8690116
Physician	Dr. Mahendra Perera	Collection Date	NA
Customer	MCC18718-Aegle Omics Private Limited	Sample Received Date	04-09-2024 03:30 PM
Report Date	06-09-2024 09:45 PM	Report Status	Final

Lab/Biopsy No : MBH-4307/24

Clinical Details : Ca. Endometrium.

Specimen received : 2 blocks. Hysterectomy specimen blocks.

Gross examination : Received two paraffin blocks No XH1632 - N, Q. From Lanka Hospitals. For IHC.
IHC done on N and Q blocks.

Immunohistochemistry (IHC) Testing for Mismatch Repair (MMR) Proteins.

Immunohistochemistry Microscopy :

IHC Markers	Pattern of expression
1. MLH1	Intact nuclear expression
2. MSH2	Intact nuclear expression
3. MSH6	Intact nuclear expression (Weak)
4. PMS2	Intact nuclear expression (Weak)

Background nonneoplastic tissue / internal control with intact nuclear expression : Yes

Impression:

Intact DNA mismatch repair (MMR) function within tumor (MMR proficient).

NOTE : Tumor is poorly preserved.

Medgenome Labs Ltd
Sy No 94/1C and 94/2, Tower-1, Veerasandra Village,
Attibele Hobli, Electronic City, Phase-1, Bangalore,
Karnataka, 560100.

MMR by Immunohistochemistry - Test Report

Patient Name	S A Shiranee M F Senevirathne	Order ID	1042163
Age / Gender	76 Years / Female	Sample ID	8690116
Physician	Dr. Mahendra Perera	Collection Date	NA
Customer	MCC18718-Aegle Omics Private Limited	Sample Received Date	04-09-2024 03:30 PM
Report Date	06-09-2024 09:45 PM	Report Status	Final

Note:

Appropriate dual control tissue run with the test is satisfactory. Reagents used are as follows **Anti MLH1(GM011 clone)** mouse monoclonal antibody , **Anti MSH2 (RED2 clone)** rabbit monoclonal antibody , **Anti-MSH6 (EP49 clone)** rabbit monoclonal antibody , **Anti PMS2 (EP51 clone)** Rabbit monoclonal antibody .

This assay has not been validated on decalcified tissue and result should be interpreted with caution given the likelihood of false negativity of decalcified specimen. Specimen should be processed by routine tissue processing method. Inappropriate fixation (nonformalin) and processing may give erroneous result. The performance characteristics of these assays have been determined by MedGenome. Performance characteristics refer to the analytical performance of the test.

Interpretation of IHC MMR:

No loss of nuclear expression of mismatch repair (MMR) proteins : Low probability of microsatellite instability-high (MSI-H).

Loss of nuclear expression of MLH1 and PMS2: testing for methylation of the MLH1 promoter and/or mutation of BRAF is indicated (the presence of a BRAF V600E mutation and/or MLH1 methylation suggests that the tumor is sporadic and germline evaluation is probably not indicated; absence of both MLH1 methylation and of BRAF V600E mutation suggests the possibility of Lynch syndrome, and sequencing and/or large deletion/duplication testing of germline MLH1 may be indicated)*

Loss of nuclear expression of MSH2 and MSH6: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline MSH2 may be indicated, and, if negative, sequencing and/or large deletion/duplication testing of germline MSH6 may be indicated)*

Loss of nuclear expression of MSH6 only: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline MSH6 may be indicated)*

Loss of nuclear expression of PMS2 only: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline PMS2 may be indicated)*

* There are exceptions to the above IHC interpretations. These results should not be considered in isolation, and clinicalcorrelation with genetic counseling is recommended to assess the need for germline testing.

Medgenome Labs Ltd
Sy No 94/1C and 94/2, Tower-1, Veerasandra Village,
Attibele Hobli, Electronic City, Phase-1, Bangalore,
Karnataka, 560100.

MMR by Immunohistochemistry - Test Report

Patient Name	S A Shiranee M F Senevirathne	Order ID	1042163
Age / Gender	76 Years / Female	Sample ID	8690116
Physician	Dr. Mahendra Perera	Collection Date	NA
Customer	MCC18718-Aegle Omics Private Limited	Sample Received Date	04-09-2024 03:30 PM
Report Date	06-09-2024 09:45 PM	Report Status	Final

Explanatory Notes

Mismatch Repair Testing: Microsatellite instability and Immunohistochemistry

Detection of defective mismatch repair in colorectal carcinomas is important for detection of Lynchsyndrome (hereditary nonpolyposis colorectal cancer syndrome [HNPCC]), which accounts for approximately 2% to 3% of all colorectal carcinomas and has clinical implications for treatment of the affected patient and family members. Microsatellite instability (MSI) testing can be used to cost-effectively screen colorectal cancer patients for possible Lynch syndrome. Patients with a microsatellite instability-high (MSI-H) phenotype that indicates mismatch repair deficiency in their cancer may have a germline mutation in one of several DNA mismatch repair (MMR) genes (eg, MLH1, MSH2, MSH6, or PMS2) or an altered EPCAM (TACSTD1) gene. After appropriate genetic counseling, patients may want to consider testing to identify the causative heritable abnormality.

An MSI-H phenotype is more frequently observed in sporadic colorectal cancer (about 15% of cases) due to somatic abnormalities, usually hypermethylation of the MLH1 gene promoter. The specificity of MSI testing can be increased by using it primarily on at-risk populations, such as colorectal cancer patients younger than 50 years, or patients with a strong family history of Lynch associated tumors (eg, colorectal, endometrial, gastric, or upper urinary tract urothelial carcinoma), but with sacrifice of sensitivity, since a sizeable minority of cases lacks these clinical characteristics.

MSI testing of tumor DNA is generally performed with at least 5 microsatellite markers, generally mononucleotide or dinucleotide repeat markers. In 1998, a National Institutes of Health consensus panel proposed that laboratories use a 5-marker panel consisting of 3 dinucleotide and 2 mononucleotide repeats for MSI testing. Recent data suggests that dinucleotide repeats may have lower sensitivity and specificity for identifying tumors with an MSI-H phenotype. As a consequence, there has been a move towards including more mononucleotides and fewer dinucleotides in MSI testing panels. Many laboratories now use a commercially available kit for MSI testing that utilizes 5 mononucleotide markers.

MSI testing is frequently done in conjunction with immunohistochemical (IHC) testing for DNA MMR protein expression (ie, MLH1, MSH2, MSH6, and PMS expression). If DNA MMR IHC has not been performed, this testing should be recommended for any case that shows an MSI-H phenotype, because this information will help identify the gene that is most likely to have a germline mutation (eg, a patient whose tumor shows loss of MSH2 and MSH6 expression, but retention of MLH1 and PMS2 expression, is likely to have an MSH2 germline mutation). If the results of DNA MMR IHC and MSI testing are discordant (eg, MSI-H phenotype with normal IHC or abnormal IHC with MSS phenotype), then the laboratory should make sure that the same sample was used for MSI and IHC testing and that there was no sample mix-up. However, MSI-H may not occur in colorectal cancers of patients with germline MSH6 mutation.

Intact expression of all 4 proteins indicates that MMR enzymes tested are intact but does not entirely exclude Lynch syndrome, as approximately 5% of families may have a missense mutation (especially in MLH1) that can lead to a nonfunctional protein with retained antigenicity. Defects in lesser-known MMR enzymes may also lead to a similar result, but this situation is rare.

Any positive reaction in the nuclei of tumor cells is considered as intact expression (normal), and it is common for intact staining to be somewhat patchy. An interpretation of expression loss in tumor cells should be made only if a positive reaction is seen in internal control cells, such as the nuclei of stromal, inflammatory, or nonneoplastic epithelial cells. Loss of expression of MLH1 may be due to Lynch syndrome or methylation of the MLH1 promoter region (as occurs in sporadic MSI colorectal carcinoma). Genetic testing is ultimately required for this distinction, although a specific BRAF gene mutation (V600E) is present in many sporadic cases, but not familial cancers. Loss of MSH2 expression strongly suggests Lynch syndrome. PMS2 loss is often associated with loss of MLH1 and is only independently meaningful if MLH1 is intact. MSH6 is similarly related to MSH2. One should also keep in mind that nucleolar staining or complete loss of MSH6 staining has been described in colorectal cancer cases with prior radiation or chemotherapy, and a significant reduction of MSH6 staining has been described in a small percentage of colorectal carcinomas with somatic mutations of the coding region microsatellites of the MSH6 gene in MLH1/PMS2-deficient carcinomas.

Enclosed: 2 blocks

Medgenome Labs Ltd
Sy No 94/1C and 94/2, Tower-1, Veerasandra Village,
Attibele Hobli, Electronic City, Phase-1, Bangalore,
Karnataka, 560100.

MMR by Immunohistochemistry - Test Report

Patient Name	S A Shiranee M F Senevirathne	Order ID	1042163
Age / Gender	76 Years / Female	Sample ID	8690116
Physician	Dr. Mahendra Perera	Collection Date	NA
Customer	MCC18718-Aegle Omics Private Limited	Sample Received Date	04-09-2024 03:30 PM
Report Date	06-09-2024 09:45 PM	Report Status	Final

Approved By

Dr. Rakshith V
Pathologist
KMC95334

*****End of Report*****

Medgenome Labs Ltd
Sy No 94/1C and 94/2, Tower-1, Veerasandra Village,
Attibele Hobli, Electronic City, Phase-1, Bangalore,
Karnataka, 560100.

CONDITIONS OF LABORATORY TESTING AND REPORTING

Medgenome Labs Ltd, Bangalore, Karnataka, India

- Laboratory results should be used with other clinical information to determine a final diagnosis.
- In case of unexpected test results please contact the laboratory. We will investigate and repeat analysis if possible.
- The medical report must be viewed and reproduced as a whole
- This medical report is not intended for medico-legal purposes.
- The medical report is to be interpreted and used by medical personnel only
- Assays are performed and reported in accordance with the stated schedule.
- There may be circumstances beyond our control that delay results, e.g., invalid assay run.
- The results of a laboratory test are dependent on the quality of the sample as well as the assay procedure.
- A requested test may not be carried out if:
- Sample is insufficient or inappropriate
- Sample quality is unsatisfactory
- Request for testing is withdrawn by the ordering doctor or patient
- There is discord between the labelling of the sample container and the name on the test requisition.
- For any query contact customer support : +91(0)8067154932/33
