Immunohistochemistry Screening for Mismatch Repair (MMRSCR) Gene Mutations

Intermountain Healthcare has instituted a system-wide policy (supported by SelectHealth) in which all colorectal tumor resection specimens are sent to ARUP for immunohistochemical staining for the presence of the proteins associated with mismatch repair (MMR) genes. The test is named MMRSCR (MMR Screen). Abnormal immunohistochemical screening results indicate a strong likelihood for Lynch syndrome, with certain important exceptions. A mutation in an MMR gene results in abnormal or absent protein that decreases mismatch repair efficiency. The mismatch repairs include: ***MLH1, MSH2, PMS2, and MSH6.***

Although the effectiveness of screening and surveillance strategies is unproven in controlled clinical trials for any of these syndromes, the high cancer risk warrants screening, and reasonable recommendations can be made. Please see the GeneInfo sheet on Familial Colorectal Cancer: Lynch syndrome.

Alert: Currently all tumor resection specimens of colorectal cancer at the following hospitals are screened with MMRSCR immunohistochemistry for mismatch repairs associated with LS:
Urban Central Region LDS, IMED, Altaview **Northern Region** McKay Dee, Logan Regional
All abnormal MMRSCR tests will be reported to Familial Cancer Counseling automatically.

Immunohistochemistry (MMRSCR) of tumor tissue. MMRSCR detects the presence or absence of the protein products expressed by mismatch repair genes. The protein products form dimers in the tissue and are often measured as both absent if the MLH1 or MSH2 proteins are missing. *MLH1* somatic mutations are often found in sporadic colon cancer and can be distinguished by the presence of a *BRAF* mutation. The immunohistochemistry result will imply whether the tumor is microsatellite stable (MSS) or instable (MSI). Tumors that show MSI are less likely to be sporadic and more likely to indicate LS. MSI will not indicate which MMR gene is involved in causing LS in that individual.

IHC staining pattern	Somatic mutation testing	
MLH1/PMS2 absent	*BRAF* mutation positive	sporadic not LS
MLH1/PMS2 absent	*MLH1* methylation positive	sporadic not LS
MLH1/PMS2 absent	Normal *BRAF* and methylation	likely LS
PMS2 absent		likely LS
MSH2/MSH6 absent		likely LS
MSH6 absent		likely LS

Mutations in *MLH1* and *MSH2* account for approximately 90% of families with LS

Mutations in *MSH6* account for approximately 7%-10% of families with LS
Mutations in *PMS2* account for fewer than 5% of families with LS

Individuals with MMRSCR results suggesting the likelihood of LS should be referred for Genetic Counseling.

Action: Identify patients at risk for LS. In patients with CRC, monitor for abnormal MMRSCR result indicating increased chance for LS. Refer patients with abnormal MMRSCR for genetic counseling. Strong family history of colon and other cancers, as indicated by Amsterdam or Bethesda criteria, should prompt referral to genetic counseling for more in-depth cancer risk assessment. See Lynch syndrome GeneInfo for more details.

801-507-3833 Familial Cancer Counseling.

Resources:

- ARUP Physician Consult: Immunohistochemistry testing for Lynch/HNPCC (http://www.arupconsult.com/Topics/LynchSyndrome.html)
- GeneReview – Lynch syndrome (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review/disease/Lynch%20Syndrome?db=genetests&search_param=contains)
- Genetics Home Reference – Lynch syndrome (http://ghr.nlm.nih.gov/search?query=Lynch+Syndrome&Search=Search)