Lynch Syndrome Mismatch Repair (MMR) Gene Mutations

Also known as: Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

Lynch syndrome, often called hereditary nonpolyposis colorectal cancer, is a type of inherited cancer of the digestive tract, particularly the colon (large intestine) and rectum. People with LS have an increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, skin, and prostate. Women with this disorder also have a high risk of cancer of the endometrium (lining of the uterus) and ovaries. Even though the disorder was originally described as not involving noncancerous (benign) growths (polyps) in the colon, people with LS may occasionally have colon polyps. In individuals with this disorder, colon polyps occur at an earlier age than in the general population. Although the polyps do not occur in greater numbers than in the general population, they are more likely to become cancerous. Colon cancer tumors can be screened with immunohistochemistry (MMRSCR) to detect the presence or absence of mismatch repair gene proteins. An abnormal MMRSCR can signal likely LS.

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 should prompt referral to genetic counseling for more in-depth cancer risk assessment. Screen using Amsterdam or Bethesda criteria. 801-507-3833 Familial Cancer Counseling

Lynch syndrome (LS) is an inherited colorectal cancer syndrome.

- Population risk for colon cancer development is about ~6%
- Individuals with LS have lifetime cancer risk of between 70 - 80%
- 50% of women with LS will develop endometrial cancer
- 10% will develop ovarian cancer
- 2 to 5% of all colorectal cancer cases and about 2 percent of uterine cancer due to LS
- 20 to 40% of LS patients have been reported to develop metachronous (multiple primary tumors) colorectal cancer
- Overall five-year survival rates in CRC patients due to LS is better than that seen in sporadic colorectal cancer

Pathology characteristics:

- Adenomas tend to be larger, flatter, are more often proximal,
- High-grade dysplasia and/or villous histology than sporadic adenomas
- The adenoma-carcinoma sequence is thought to progress much more rapidly in Lynch syndrome and new cancers have occurred within two to three years after what appeared to be a negative colonoscopy.
- May contain an intense “Crohn's-like” lymphocytic infiltrate at their periphery
- More commonly mucinous

Caution: Tumor histology is not adequate to screen patients for LS.

The Genetics of LS: Mismatch Repair (MMR) genes

LS is due to mutations in genes called mismatch repair genes (MMR). MMR proteins maintain genomic integrity by correcting base substitution mismatches and small insertion-deletion mismatches that are generated by errors in base pairing during DNA replication. Normal mismatch repair requires the coordinated function of several different proteins. Mutations in an MMR gene results in abnormal or absent protein that decreases mismatch repair efficiency.

The mismatch repair genes include: MLH1 MSH2 PMS2 MSH6

Patients with LS usually have a germline mutation in one allele (copy) of a MMR gene and the second allele is inactivated in the somatic tumor tissue by sporadic mutation, loss of heterozygosity, or silencing by promoter hypermethylation. Immunohistochemistry screening of MMR proteins in colorectal tumor specimens will identify the likely MMR gene and implies whether the tumor is microsatellite stable or instable.

See GeneInfo sheet on MMRSCR: Immunohistochemistry screening for LS.

Alert: Currently all tumor resection specimens of patients with colorectal cancer at the following hospitals are screened with MMRSCR immunohistochemistry for Lynch syndrome:
Urban Central Region LDS, IMED, Altaview **Northern Region** McKay Dee, Logan Regional

Genetic Counseling and Genetic Testing for LS

LS is inherited in an autosomal dominant manner. The majority of individuals diagnosed with LS have inherited the condition from a parent. However, because of incomplete penetrance, variable age of cancer development, cancer risk reduction as a result of screening or prophylactic surgery, or early death, not all individuals with a MMR gene mutation have a parent who had cancer. Each child of an individual with LS has a 50% chance of inheriting the mutation. Mutations in MMR genes are passed to children in germ cells at the time of conception.

Benefits of genetic testing in high risk families

- more accurate diagnosis
- risk assessment of family members
- specific targeting of clinical screening and surveillance protocols to gene carriers
- Family members who did not inherit the mutation and do not need an intensive surveillance program.

Screening Recommendations for patients with LS:

Colon

- Colonoscopy every one to two years beginning between age 20 and 25 years or ten years before the earliest age of diagnosis in the family

- Colonoscopy is recommended rather than flexible sigmoidoscopy because of the predominance of proximal colon cancer.

Gynecologic

- Endometrial cancer and ovarian cancer surveillance is less well established than that for colon cancer
- Many endometrial cancers can be diagnosed at early stages on the basis of symptoms, women should be educated about the signs of endometrial cancers
- Annual pap smear and pelvic examination
- Annual transvaginal ultrasound examination, office endometrial sampling, and CA-125 blood test beginning between age 30 and 35 years (or 5-10 years before the earliest diagnosis in the family) can be considered
- For premenopausal women, this screening is recommended between days one and ten of the menstrual cycle.

Stomach and duodenum Upper endoscopy surveillance is available to screen for gastric and duodenal cancer. Approximately 50% of the small bowel cancers have been noted to be located in the duodenum, suggesting that upper endoscopy may be useful for screening.
Hepatobiliary tract At this time, no specific screening recommendations for hepatobiliary tract cancers exist.
Urinary tract Annual urine cytology is an approach for screening for urinary tract cancers. There are no data indicating that such screening leads to earlier diagnosis or improved outcome, but the testing is inexpensive and associated with minimal risks. The optimal age to begin screening for urinary tract cancers has not been determined, but the risk for developing such types of cancer before age 30 years is low.
Brain/central nervous system At this time, no specific screening recommendations for brain tumors exist.

Alert: Family members who have inherited a MMR mutation should talk with their healthcare providers about the onset of colorectal cancer screening, generally recommended to start in the twenties depending on the MMR gene and the family presentation of cancer.

Resources:

- GeneTests (Funded by the National Institutes of Health)
- Uptodate