Lynch syndrome/hereditary non-polyposis colon cancer fact sheet

Clinical features
Lynch syndrome (LS) is caused by a mutation in a mismatch repair (MMR) gene. Individuals with LS are at increased risk for colon and other cancers, including gastric, urinary tract, brain, small bowel, pancreatic, hepatobiliary and sebaceous carcinoma. Women with LS are at increased risk for endometrial and ovarian cancer.

Diagnosis of LS
An individual should meet Amsterdam II criteria or have a mutation that is identified by molecular genetic testing of the MMR genes.

Clinical diagnosis of LS: The Amsterdam II criteria define the minimum requirements for a clinical diagnosis of Lynch syndrome.

There should be at least three relatives with a Lynch/HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter or renal pelvis) *and* …

- One should be a first-degree relative to the other two
- At least two successive generations should be affected
- At least one should be diagnosed before age 50
- Familial adenomatous polyposis should be excluded
- Tumors should be verified by pathological examination

Inheritance
Autosomal dominant

Gene(s)
Mismatch repair genes
MLH1 & MSH2 (mutation present in about 90 percent of LS families)
MSH6 (mutation present in about 7–10 percent of LS families)
PMS2 (mutation present in <5 percent of LS families)

Non-mismatch repair genes
EPCAM (mutation present in 1–3 percent of LS families)

Genetic testing
Direct gene testing is available commercially. To identify colorectal cancer patients who may have LS, the current recommendations are to begin by ordering microsatellite instability (MSI) or immunohistochemistry (IHC) testing on the tumor sample. This can be performed by a pathologist on archived tumor blocks from a surgical specimen. These tests detect either an increased number of

microsatellite repeats (MSI, a hallmark of impaired mismatch repair gene activity), or the absence of the protein products of the mismatch repair genes (IHC). MSI/IHC have known utility for colorectal and endometrial cancers but are not routinely recommended for other cancers. If either test is positive, meaning that the mismatch repair genes appear to be impaired, then continue on to genetic testing that can determine which mismatch repair gene is mutated. Whenever possible, begin this genetic testing on an affected family member. The identification of a mutation confirms the diagnosis of LS. If a mutation is not identified, a diagnosis of LS can neither be confirmed nor ruled out; this result must be interpreted in the context of the patient's MSI/IHC results, family and personal history and test limitations. See "Overview of testing for Lynch syndrome tool" for more information.

Colon cancer risk			
	General population	Lynch syndrome	Mean age at cancer onset (LS)
Male	5.6%	28–75%*	44–61 years
Female	5.3%	24–52%*	44–61 years

*lower risks w/MSH6, PMS2 gene mutations

Associated cancer risks*			
Type of cancer	General population	Lynch syndrome	Mean age at cancer onset (LS)
Endometrium	2.7%	27–71%	46–62 years
Ovary	1.6%	3–13%	43 years
Other (stomach, hepatobilliary, urinary tract, etc.)	<1%	Stomach: 2–19% Urinary tract: 1–12% Others: 1–7%	Variable

*Increased risks for additional primary colon cancers

Non-cancer findings: keratoacanthomas, sebaceous adenomas

Screening recommendations (See "Screening guidelines tool"):

1. Colonoscopy: every one to two years starting at age 20–25 or two to five years prior to the earliest colon cancer in the family if diagnosed under age 25.
2. If colon cancer is found, consider removal of entire colon and continue annual screening for rectal cancer.
3. Consider prophylactic removal of the colon in cases where regular screening with colonoscopy cannot be performed.
4. Females: consider annual endometrial sampling and transvaginal ultrasound.
5. Consider prophylactic hysterectomy with bilateral salpingo-oophorectomy after childbearing is complete.
6. Consider annual urinalysis.
7. Consider EGD with extended duodenoscopy and polypectomy at two to three year intervals beginning at age 30.

Screening references:

NCCN Colorectal Cancer Screening Guidelines, V.2.2011.
nccn.org/professionals/physician_gls/f_guidelines.asp

ACG Guidelines for Colorectal Cancer Screening 2009.
http://s3.gi.org/physicians/guidelines/CCSJournalPublicationFebruary2009.pdf

Vasen, H., Watson, P., Mecklin, J.-P., & Lynch, H. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology*, 116(6), 1453–1456.