

GENETICS OF COLORECTAL CANCER: HEREDITARY ASPECTS

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Could this be
hereditary
Colon Cancer

Magnitude of the Problem

Annual worldwide incidence of CRC is 1,023,152*:

- Lynch syndrome (LS) accounts for \approx 2-5% (20,460-51,160 cases).
- $<$ 1% (10,230 cases) constitute FAP.
- \approx 20% (204,630 cases) are familial (2 or more first-degree relatives with CRC).

*International Agency for Research on Cancer. Globocan 2002. Available at: <http://www-dep.iarc.fr/>.

Cardinal Features of Lynch Syndrome

- Family pedigree shows autosomal dominant inheritance pattern for syndrome cancers.
- Earlier average age of CRC onset than in the general population:
 - Lynch syndrome: 45 years;
 - general population: 63 years.
- Accelerated carcinogenesis, i.e., shorter time for a tiny adenoma to develop into a carcinoma:
 - Lynch syndrome: 2-3 years;
 - general population: 8-10 years.
- High risk of additional CRCs:
 - 25-30% of patients who have surgery for a LS-associated CRC will have a second primary CRC within 10 years, if surgery was $<$ a subtotal colectomy.
- Increased risk for certain extracolonic malignancies:
 - endometrium (40-60% lifetime risk for ♀ carriers);
 - ovary (12% lifetime risk for ♀ carriers);
 - stomach (higher risk in families from Orient);
 - small bowel;

Magnitude of the Problem

Question: Why are these figures of such significant public health impact?

Answer: Each hereditary cancer comes from a family that could benefit immensely from genetic counseling.

DNA testing, surveillance, and highly-targeted management are the key!

Cardinal Features of Lynch Syndrome

- Increased risk for certain extracolonic malignancies (continued):
 - hepatobiliary tract;
 - pancreas;
 - upper uroepithelial tract (transitional cell carcinoma of the ureter and renal pelvis);
 - brain (in Turcot's syndrome variant of LS);
 - sebaceous adenomas, sebaceous carcinomas, multiple keratoacanthomas (in Muir-Torre syndrome variant of LS).
- Differentiating pathology features of LS CRCs:
 - more often poorly differentiated;
 - excess of mucoid and signet-cell features;
 - Crohn's-like reaction;
 - significant excess of infiltrating lymphocytes within the tumor.
- Increased survival from CRC.
- *Sine qua non* for diagnosis is identification of germline mutation in MMR gene (most commonly *MLH1*, *MSH2*, *MSH6*) segregating in the family.

Targeted CRC Screening

Screening is melded to LS's natural history:

Proximal location → colonoscopy

Early age of onset → beginning at age 25

Accelerated carcinogenesis → every 1-2 yrs < age 40, then annually

Pattern of extra-clonic cancers → targeted screening

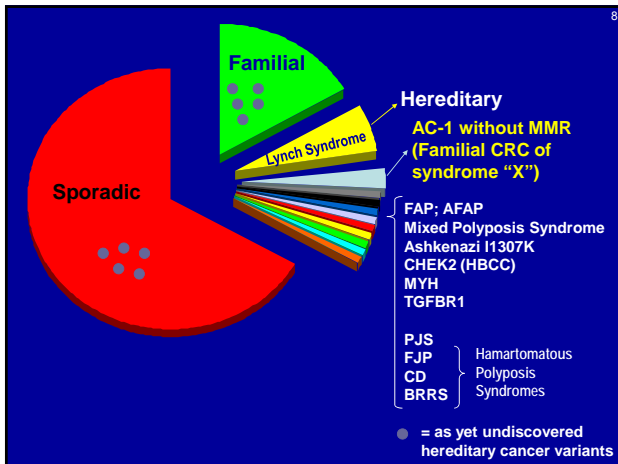
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Lynch Syndrome: Genotypic Heterogeneity

Clinical cancer phenotypes differ with each of the MMR mutations:

1. *MSH2* has ↑ extracolonic cancer types and ↑ Muir-Torre syndrome
2. *MLH1* may have ↑ CRC expression.
3. *MSH6* may be more "benign" with ↓ CRC but ↑ endometrial cancer.

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Recently described LS mutations

PMS2 mutations contribute significantly to LS*.

CHEK2 1100delC Is a Susceptibility Allele for HNPCC-Related Colorectal Cancer**.

Germline Allele-Specific Expression of *TGFBR1* Confers an Increased Risk of Colorectal Cancer***.

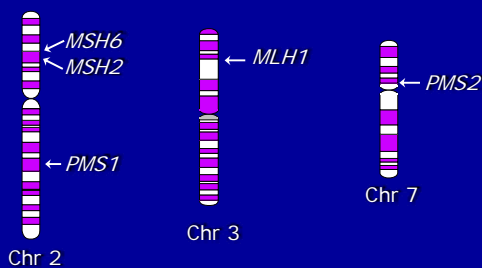
*Senter et al. *Gastroenterology* 135:419-428, 2008.

**Wasielewski et al. *Clin Cancer Res* 2008;14(15) August 1, 2008

***Valle et al. *Science* 321:1361-1365, 2008.

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Genetic Heterogeneity in HNPCC



HNPCC is associated with germline mutations in any one of at least five genes

Lynch syndrome (LS) and Mismatch Repair (MMR) Genes: What Are the Risks?

A new era for genetic counseling evolved thanks to the cloning of *MSH2*, *MLH1* and *MSH6*.

Prior to MMR mutation discovery we had to rely solely on an individual's family history.

Now we can determine lifetime risks for CRC and extra colonic cancers by MMR testing.

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Molecular Diagnosis of LS: Toward a Consensus

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If tumor is MSI-positive, IHC is then done to direct mutational testing to a specific MMR gene, which MSI alone cannot do.*

If tumor is MSS, must weigh low probability of an informative IHC test and cost of performing it.**

*Engel et al. *Int J Cancer* 118:115-122, 2006.

**Lynch et al. *J Natl Cancer Inst* 99:261-263, 2007.

Familial CRC

Familial clustering of CRC, like that for carcinoma of the breast and stomach, has been discussed for more than 100 years.

What does it mean from the standpoint of risk?

Best answer – First-degree relative of CRC affected has 2-3 fold excess risk for CRC compared to population expectations.

But is syndrome X different?

Answer – Risk remains elusive!

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BRAF V600E mutation and LS

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BRAF V600E mutation can sort this out since when detected it excludes LS and contributes to improved cost-effectiveness of genetic testing for LS.

**Clin Gastroenterol Hepatol* 6:206-214, 2008.

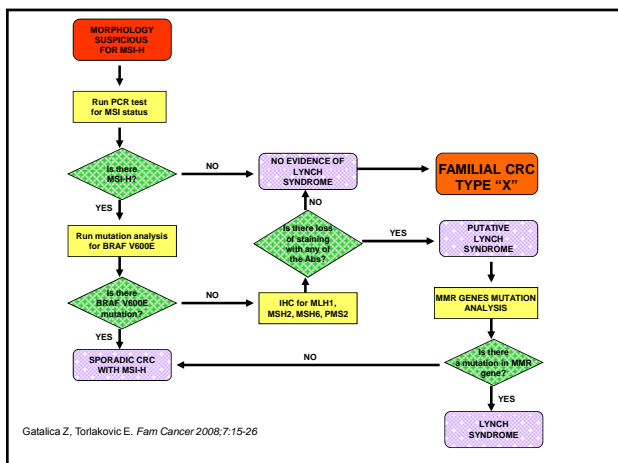
Familial Syndrome "X"

Amsterdam Criteria positive but lacking MSI and MMR mutations will constitute ~ 40% of those AC-I without MMR mutations and therein referred to as familial CRC type X.*

- 1) CRC > left side
- 2) ↓ CRC and extra colonic CRC
- 3) Later age CRC onset
- 4) Molecular genetics (MSI and IHC or MMR mutation) **ABSENT!**

*Lindor et al. *JAMA* 293:1979-1985, 2005.

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Deletion of the 3' Exons of TACSTD1*

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Deletion encompassing the *TACSTD1* silencing *MSH2* will likely be important in characterizing some LS families who have loss of *MSH2* on IHC, but for whom no identifiable alteration is found in the *MSH2* gene.

*Ligtenberg et al. *Nat Genet* 41:112-117, 2009.

Kobelka. *Clin Genet* 75:522-526, 2009.

Deletion of the 3' Exons of TACSTD1*

Conclusion:

Instead of an “uninformative negative” result from *MSH2* mutation testing, such families would have an explanation for their family cancer history.

Family members with a *TACSTD1* deletion would be recommended to follow high-risk cancer screening guidelines; those without the deletion would not be at increased risk and would be recommended to follow general population screening guidelines.

*Ligtenberg et al. *Nat Genet* 41:112-117, 2009.
Kobelka. *Clin Genet* 75:522-526, 2009.

Who Should Be Sent for Genetic Testing in Hereditary Colorectal Cancer Syndromes?

Henry T. Lynch, C. Richard Boland, Miguel A. Rodriguez-Bigas, Christopher Amos, Jane F. Lynch, and Patrick M. Lynch

J Clin Oncol 25:3534-3542, 2007.

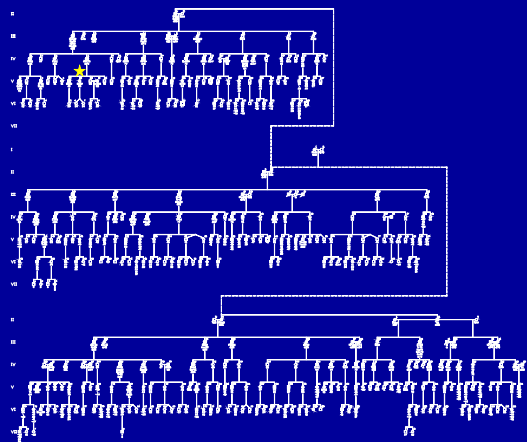
Acknowledgement

Steve Thibodeau, PhD., and Douglas Riegert-Johnson, MD., Mayo Clinic

Discovered the *TACSTD1* mutation in the following highly extended kindred.

Who Should Be Tested?

1. Pedigree consistent with hereditary colorectal cancer (CRC) syndrome;
2. Known germline mutation predisposing to cancer;
3. Patients at acceptable high cancer risk status;
4. Presence of cancer syndrome stigmata (phenotype): e.g., polyposis in FAP;
5. Genetic counseling, risks/benefits understood;
6. Consent given;
7. Results: full explanation of surveillance/management advice.



Adjuvant therapy 5FU in MSI high patients

Meta-analysis shows 5FU ineffective in MSI high patients (Lynch syndrome)

Guidelines do not recommend using MSI status to determine whether to use chemotherapy

Search for LS Among CRC Affecteds*

Among 500 CRC patients, 18 (3.6%) had LS.

Of these 18:

- 18 (100%) had MSI-H CRCs;
- 17 (94%) were correctly predicted by IHC;
- only 8 (44%) were dx < 50 years;
- only 13 (72%) met the revised Bethesda guidelines.

*Hampel et al. *J Clin Oncol* 26:5783-5788, 2008. 25

Genetic Testing and Cancer Control in Lynch Syndrome

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group* constructed a chain of evidence linking genetic testing for LS in patients with newly dx CRC with improved health outcomes in their relatives.

Does it work?

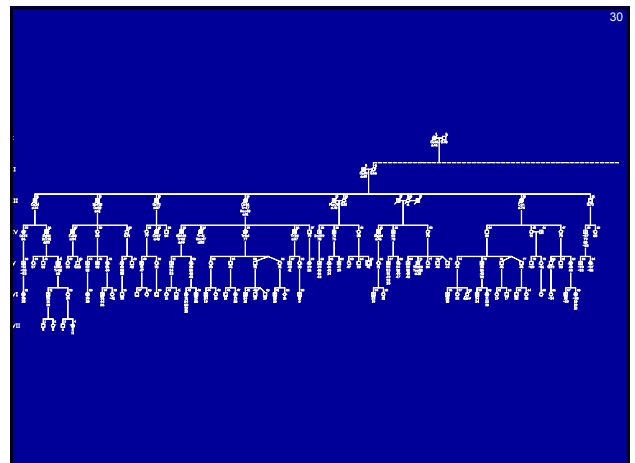
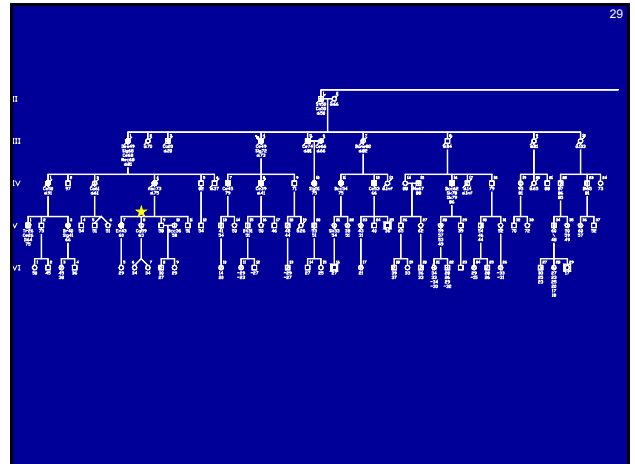
**Genetics in Medicine* 11:35-41, 2009. 26

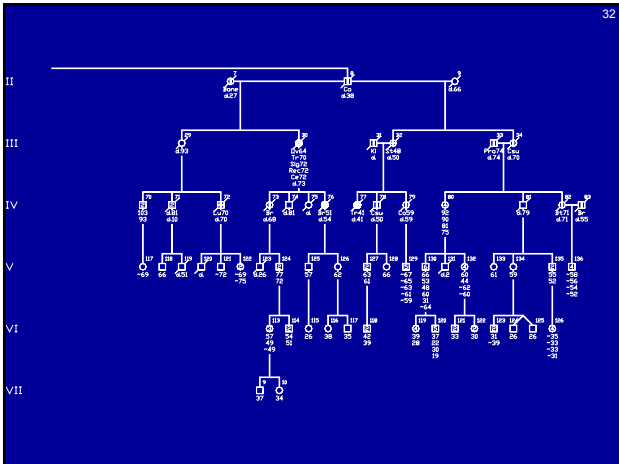
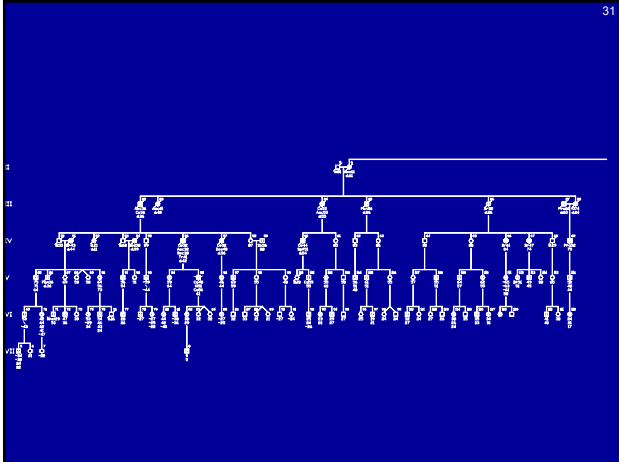
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) of Lynch Syndrome*

Conclusion:

E W G concluded that there was moderate certainty that such a testing strategy would provide moderate population benefit.

**Genetics in Medicine* 11:35-41, 2009. 27





Search for LS Among CRC Affecteds*

One of every 35 patients with CRC has LS; each has at least 3 relatives with LS, all of whom can benefit from increased cancer surveillance/management.

IHC almost equally sensitive as MSI; however, IHC is more readily available and helps to direct gene testing.

Limiting CRC tumor analysis to patients who fulfill Bethesda guidelines would fail to identify 28% (or one in four) cases of LS.

*Hampel et al. *J Clin Oncol* 26:5783-5788, 2008.

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Family Information Service (FIS)

Cost-effective and highly efficient way of educating and counseling all available family members from a geographic catchment area during a single setting.

Makes best use of physician's time and effort, has group therapy potential and patients welcome it.

Value of testing all CRC cases

Hampel et al.* note that it is remarkable that of the 153 individuals (44 probands and 109 relatives) identified with LS as part of her study, only one had been previously diagnosed with LS.

It would be valuable to translate this into its morbidity and mortality reduction.

*Hampel et al. *J Clin Oncol* 26:5783-5788, 2008.

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Value of testing all CRC cases*

An extremely telling statement:

“It is a sign about how poorly obtaining and assessing family history of cancer works in practice and the low referral rate.”

*Hampel et al. *J Clin Oncol* 26:5783-5788, 2008.

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LYNCH SYNDROME and its HETEROGENEITY, A hereditary CRC Model

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Table 2. Relatives Tested in the Entire Study Cohort

Relationship	Mutation Positive	Mutation Negative	Total Tested
First degree	52	47	99
Second degree	28	36	64
Beyond second degree	29	57	86
All	109	140	249

Hampel et al. *J Clin Oncol* 26:5783-5788, 2008.

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Who Should Be Tested?

Referral to medical geneticist/center of hereditary cancer expertise:

1. When physician lacks expertise, referral should be made to a cancer genetics center.
2. Key medical/genetic/genealogic findings made available to referral center.
3. Patient/family acceptance.
4. Candidate for DNA testing accepts, is tested, and results are fully explained in genetic counseling setting.

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Molecular Genetics and Lynch Syndrome

≈ 15% of all CRCs show MSI:

- Most not caused by Lynch syndrome.
- Acquired silencing (epigenetic inactivation) of *MLH1* gene by methylation of promoter.
- Immunohistochemistry (IHC) useful for identifying protein loss (*MSH2*, *MLH1*).

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Colon Cancers with increased MSI

More right sided
Poorly differentiated
Lymphocytic infiltration
Mucinous

Better prognosis (untreated)

– 35% improvement in survival

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ECOG 5202 Current Trial Stage II (T3NO)

Area major controversy adjuvant treatment

- Stage II colon cancer

MSI high patients receive no chemo

Other patients randomized

- Folfox +/- Bevacizumab (anti-VEGF)