

Lynch Syndrome

A paradigm of predictive personalized medicine

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Lynch Syndrome

- **Dominant inheritance; high penetrance**
- **Main cancers: colorectal, endometrial**
- **Other frequent cancers: gastric, ovarian**
- **Other infrequent cancers: small bowel, uroepithelial, biliary tract, brain, pancreatic (?)**
- **Examples of cancers *not* involved: breast, lung, prostate**

Lynch Syndrome

Colorectal cancer

- **Early onset (~55 y vs ~ 68 y)**
- **Synchronous & metachronous tumors**
- **Right-sidedness**
- **Better prognosis**
- **Easy screening methods; microsatellite instability; immunohistochemistry**

Lynch Syndrome

- Is it desirable to diagnose it?
- Should it be diagnosed passively (occasional referral to genetic evaluation) or actively (by screening)?
- Is Lynch syndrome frequent enough to be screened for and who should be screened?
- Method of screening
- Problems, obstacles

Controlled 15-Year Trial on Screening for Colorectal Cancer in Families With Hereditary Nonpolyposis Colorectal Cancer

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15-year prophylactic colonoscopic screening

Järvinen et al. 1995 and 2000

	Screened n=133	Not screened n=119	
Colorectal cancer	8	19	n=0.014
Death from colorectal cancer	0	9	p<0.001
Overall deaths	10	26	p<0.001

ORIGINAL ARTICLE

Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome

Kathleen M. Schmeler, M.D., Henry T. Lynch, M.D., Lee-may Chen, M.D., Mark F. Munsell, M.S., Pamela T. Soliman, M.D., Mary Beth Clark; M.S.W., Molly S. Daniels, M.S., Kristin G. White, B.S., Stephanie G. Boyd-Rogers, R.N., Peggy G. Conrad, M.S., Kathleen Y. Yang, M.D., Mary M. Rubin, Ph.D., Charlotte C. Sun, Dr.P.H., Brian M. Slomovitz, M.D., David M. Gershenson, M.D., and Karen H. Lu, M.D.

NEJM 2006

Schmeler et al. NEJM 2006

Retrospective study of 315 pts

Hysterectomy done in 61

Salpingo-oophorectomy done in 47

- In operated pts no endometrial, ovarian or peritoneal cancer
- In unoperated pts 69 cases of endometrial cancer and 12 cases of ovarian cancer
- Prevented fraction 100%

Passive vs active diagnostics of Lynch syndrome

Passive: Refer cancer patients to genetic counseling and mutation detection after nurse or physician has detected "risk" features

Active: Screen unselected patients with simple test (MSI; IHC) or perhaps the Bethesda guidelines to identify risk individuals for mutation detection

Is Lynch syndrome frequent enough to be screened for?

Proportion of unselected cases having LS
(Columbus study 1999-2005)

Colorectal cancer	44/1566	(2.8%)
Endometrial cancer	13/562	(2.3%)

Hampel et al. *NEJM* 2005

Hampel et al. *Cancer Res* 2006

Hampel et al. *J Clin Oncol* 2008

How many family members of a newly diagnosed proband with LS will be studied for the mutation, and how many mutation carriers will be found?

Total No. of new probands	44
No. counseled so far	33
No. of family members tested	246 (7.5/proband)
No. of family members with mutation	108 (3.3/proband)
No. of family members without mutation	138 (4.2/proband)

Hampel et al *NEJM* 2005 and *J Clin Oncol* 2008

Idealized national figures, USA

Newly diagnosed CRC	150,000
Thereof LS mutation carriers (2.8%)	4,200
Family members tested (7.5/proband)	31,500
Family members mutation-positive (3.3/proband)	13,860
Family members mutation-negative (4.2/proband)	17,640
Total	
New Lynch syndrome 4,200 + 13,860	18,060
High-risk individuals returned to average risk	17,640

Hampel et al. *NEJM* 2005 and *J Clin Oncol* 2008

Problems, obstacles

- Is it harmful?
- Who will pay?
- Is it cost-effective?
- Will the health care system cope?

Summary

- Detecting LS is desirable because intensified clinical cancer surveillance saves lives
- With present-day practices only a *small* fraction of all LS is diagnosed
- Screening of *all* colorectal and endometrial cancer patients is advocated
- Immunohistochemistry of the mismatch repair genes is recommended as the primary screen
- Social, economic and health care policy circumstances need further study



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