

ESMO Conference  
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## Hereditary colorectal cancer syndromes

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## Challenging Case

- 50 y/o female, negative family history
- 18 yrs ago high rectal adk → radical resection :  
early stage T1 N0 → no further treatment
- Now : 2 small R colon adenomas (3 and 5 mm ø) with adk  
After endoscopic polypectomy, margins are infiltrated

Colectomy ?

## Challenging case: issues

1. Why do I suspect ..... ?
2. What should I suspect ?
3. How should I manage the patient ?
  - initially
  - follow-up
4. When refer to genetic counseling ?
5. How about relatives ?

## Red Flags

1. Early age of onset
2. Multiple cancers
  - same or different sites
  - synchronous or metachronous
3. Rare histology /unusual location
4. Non malignant manifestations characteristic  
of a hereditary cancer syndrome

Zbuk, *Nature Clin Pract Oncol* 2007  
Winship, *Lancet Oncol* 2008

## What should I suspect ?

- HNPCC - Lynch Syndrome (2-5 %)

Adenomas in HNPCC :

- Risk increases with age:
  - 5 % at < 35 yrs
  - 20 % at > 55 yrs
- Right colon mainly

Liljegren, *JCO* 2008

Lynch, *Fam Ca* 2008; *NCI PDQs Feb* 2009; *NCCN Jan* 2009

## Probability of carrying a HNPCC associated gene mutation

- CRC - general population (MSI + IHC → gen. test):
  - 2.8 % overall
  - 13 % if age 30-39 yrs
- Bethesda Criteria:
  - 50% if 2 criteria satisfied (age <50, multiple CRC)
  - 60% if 2 criteria + MSI

Hampel, *JCO* 2008

Lynch, *JCO* 2007

## Predictive models for HNPCC

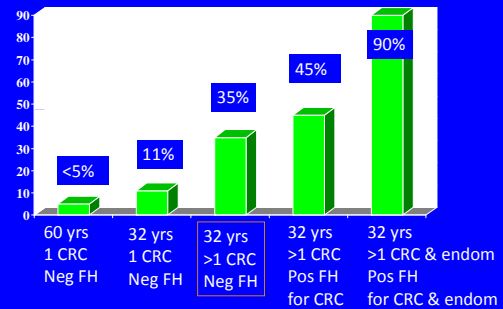
Leiden  
MMRpro  
MMRpredict  
PREMM1,2

Comparison studies:

- similar performances
- MMRpredict and PREMM1,2 best

*Pouchet, Ann Oncol 2009*  
*Green, JNCI 2009*

CRC patients  
Risk of HNPCC gene mutation  
PREMM1,2 model (*Balmana, JAMA 2006*)



## Probability of negative genetic test

- HNPCC: up to 50%
- FAP: up to 20%
- Attenuated polyposis (AFAP, MAP): > 40%

*Lynch, JCO 2007*

## How should I manage the patient initially ?

Colectomy ?

Except for diffuse polyposis syndromes:

## Familial Adenomatous Polyposis (FAP)



## How should I manage the patient initially ?

Colectomy ?

Except for diffuse polyposis syndromes:

- No OS benefit after colectomy vs endoscopic f-up <sup>(1)</sup>
- Risk of CRC after colectomy: 12% at 12 yrs <sup>(2)</sup>
- Later option
- Timing too short for pre-test and post-test counseling

*1. Al-sukni, ASCO 2009 abstr e 15059*  
*2. ASCO/SSO, JCO 2006*

### When refer to genetic counselling?

'Too much, too soon?'

- Cancer prognosis
- Anxiety → understanding & choosing

*Ardern-Jones, Eur J Ca Care 2005 (breast ca)*

+

Chemotherapy = sporadic CRC patients

*Seiden, NEJM 2007*

↓

No need for 'urgent' genetic counselling in MOST cases

### Challenging Case (cmtd)

- Right hemicolectomy. Stage I. No adj CT
- Subsequent genetic counselling: carrier of a MLH1 genetic mutation (HNPCC-linked)

↓

Annual endoscopic follow-up

*Seiden, NEJM 2007; Lynch JCO 2007*

Endometrial & ovarian cancer risk: surveillance or prophylactic surgery?

### Extra colonic cancer lifetime risk in HNPCC (Lynch Syndrome)

- > 10 %
 

Endometrial	27-71
Ovarian	3-14
Gastric	2-30
Urinary tract	1-28
Pancreatic or biliary	2-18

Median age 46-62
- < 10 %
 

Brain	1-4
Skin	4
Small bowel	2-8

*Koornstra, Lancet Oncol 2009*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

*Schmeler KM et al, 2006*

- 100% incidence reduction
- No overall mortality reduction

70% EC were stage I in the 'no surgery' group

editorials: *Offit & Kauff, NEJM 2006*  
*Lynch & Casey, Nat Clin Pract Oncol 2007*

### How should I manage the patient follow-up?

MD Anderson cost-effective analysis for Gynecologic ca in HNPCC

Best option?  
 Surveillance from 30 to 40 y/o  
 → prophylactic surgery

*Kwon, Cancer 2008*

### Surveillance for other extra colonic cancers in HNPCC

- Discordant expert opinion and low compliance (1)
- Tailor according to
  - Distribution of cancers within the family (2)
  - Type of mutation (3)
  - Anticipation (4)

(1) *Jeans, Nat Rev Clin Oncol 2009; Stadler, ASCO 2009*  
 (2) *Koornstra, Lancet Oncol 2009*  
 (3) *Clyne, Br J Ca 2009; Wijnen, Gastroenterology 2009*  
 (4) *Nilbert, JCO 2009; Gruber & Mukherjee, JCO 2009*

### Surveillance for extra colonic cancers in AFAP

- Extra colonic cancer spectrum  $\neq$  HNPCC
- 2nd most common cancer at Vater's ampulla
- Expert opinion guidelines:  
upper GI surveillance by side-view endoscopy

NCCN Jan 2009; Vasen, Gut 2008

### How should I manage the patient follow-up ?

Genetic counselling  
(appropriate pre-test and post-test process)  
Foulkes, NEJM 2008

↓

different follow-up / prevention strategies  
according to syndrome diagnosed

### Challenging case (cntd)

- Our patient asks for genetic counselling for her 25 y/o daughter
- If positive genetic testing (HNPCC).....

Benefit from surveillance?

### How about relatives ?

HNPCC  
Colorectal cancer lifetime risk  
in mutation carriers up to 80%  
Median age 45 yrs

AFAP  
Colorectal cancer lifetime risk  
in mutation carriers up to 70%  
Median age 50-60 yrs

NCCN Jan 2009; Burt, Gastroenterology 2004

### Benefit from surveillance

Colonoscopy surveillance in at risk relatives:

CRC incidence	}	↓ 60-70%
AND		
CRC mortality		

Strongest evidence of benefit  
from genetic counselling

Jarvinen, Gastroenterology 2000  
De Jong, Gastroenterology 2006  
Dove-Edwin, BMJ 2005

### How about relatives?

Colonoscopy:  
best option for CR surveillance

HNPCC guideline protocols:

- starting from age 20-25
- every 1-2 yrs

NCI PDQs Feb 2009  
NCCN Jan 2009  
InSIGHT 2007

## Conclusions

1. Complex issue
  - Multidisciplinary approach
2. Long term relationship with patients
  - Timing for genetic counselling
  - Reassessment of risk after
    - new cases in the family
    - new syndromes described
3. Resources (quality/quantity)
4. Future therapeutic options ..... ?

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JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement: The Role of the Oncologist in Cancer Prevention and Risk Assessment

*Robin T. Zou, et al*

Oncologists are well positioned to ....

**BUT**

the burden on oncologists associated with fully explaining these issues to patients will intensify