Hereditary Colorectal Cancer

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Johns Hopkins University
Disclosures

• I have no relevant financial relationships with commercial entities

• I do not reference unlabeled or unapproved uses of drugs or other products
Objectives

• Name the forms of hereditary colorectal cancer

• Understand the genetic tests which screen and diagnosis hereditary forms of colorectal cancer
Colorectal Cancer

- Second leading cause of cancer death
- 142,000 cases per year
- 51,000 deaths per year
- Medical treatment not curative
COLORECTAL CANCER

Sporadic

Hereditary
COLORECTAL CANCER

Sporadic

FAP

Lynch

Familial
Hereditary Syndromes

- Lynch Syndrome (HNPCC)
- Familial Colorectal Cancer Type X
- Familial adenomatous polyposis (FAP)
- Attenuated FAP
- MYH associated polyposis (MAP)
Lynch Syndrome
Lynch Syndrome

- Autosomal dominant disease
- Alternation of mismatch repair gene
- Proximal location of colorectal cancer
- Early age of onset
- Multiple primary malignancies
- Other family cancer
Lynch Syndrome

Dr Henry Lynch
Seminal paper 1966
Anne J. Krush, M.S.
Nomenclature

• Hereditary nonpolyposis colorectal cancer
  – Meets Amsterdam Criteria

• Lynch syndrome
  – Gene mutation known
Amsterdam Criteria

3 or more with CRC

2 generations

1 diagnosed age < 50 yrs
Amsterdam II Criteria

• Same as Amsterdam I but can substitute other LS cancers for colon cancer
COLORECTAL CANCER

LS
right sided

Sporadic
left sided
COLORECTAL CANCER

LS
right sided

Sporadic
left sided
COLORECTAL CANCER

LS
right sided

Sporadic
left sided
COLORECTAL CANCER

LS
right sided

Sporadic
left sided

64 yo
COLORECTAL CANCER

LS  right sided

Sporadic  left sided

44 yo  64 yo
Age of Diagnosis of Colorectal Cancer in LS

![Bar graph showing the age distribution of colorectal cancer diagnosis. The x-axis represents age in years, and the y-axis represents the number of cases (No.). The age ranges are <20, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80-89. The graph indicates a higher number of cases in the 30-39 and 40-49 age groups.]
Cancer Risks in LS

Cancer Risks in LS

Aarnio M et al. *Int J Cancer* 64:430, 1995

- Colorectal: 74%
- Endometrial: 60%
- Stomach: 13%
- Biliary tract: 4%
- Urinary tract: 16%
- Ovarian: 20%
- Sm. Bowel: 12%

Age (years)
Cancer Risks in LS

% with cancer

Age (years)

Colorectal 74%
Endometrial 60%
Stomach 13%
Biliary tract 4%
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Cancer Risks in LS

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Screening At-Risk Members

- Colonoscopy q 1-2 years starting age 20-25, then annually after 40 yo

- GYN exams in women annually, biopsy of endometrium and transvaginal ultrasound

- Screening for gastric and urologic cancer
Screening: Genetic Testing

- Mutation mismatch repair genes (MMR)
  - MSH2, MLH1, PMS2, MSH6
- EPCAM gene
LS Results From Failure of Mismatch Repair Genes

Base pair mismatch

Normal DNA repair

Defective DNA repair (MMR+)

\[
\begin{align*}
T & \quad C \\
C & \quad T \\
T & \quad A \\
A & \quad G \\
G & \quad C \\
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EPCAM Gene

5' EPCAM  MSH2 Promoter 3'

5' EPCAM  MSH2 Promoter 3'
EPCAM Gene

5’   EPCAM   MSH2   3’

Promoter

X  X
EPCAM Gene

5’ EPCAM X X Promoter

Methylation

MSH2

3’
EPCAM Gene

EPCAM

Promoter

Methylation

MSH2

X

X

5'

3'
GENETIC TESTING

Germline
- MSH2
- MLH1
- MSH6
- PMS2
- EPCAM

Somatic
- Microsatellite Instability
- & Immunohistochemistry

Blood
Cancer
Microsatellite Instability (MSI)

Normal

Microsatellite instability

Addition of nucleotide repeats
Immunohistochemistry

- Stain tumor for gene proteins
- Pursue absent of proteins
BRAF Mutation Testing

- Tissue test
- Somatic BRAF mutations
- BRAF mutation not found in Lynch sydr.
Revised Bethesda Criteria

- CRC less than 50 yo
- CRC and HNPCC related cancer
- CRC Crohns like less than 60 yo
- CRC and 1° relative CRC less than 50 yo
- CRC and two 1° or 2° degree relatives with any HNPCC related tumor
Revised Bethesda Criteria

- CRC less than 50 yo
- CRC and HNPCC related cancer
- CRC Crohns like less than 60 yo
- CRC and 1\textsuperscript{o} relative CRC less than 50 yo
- CRC and two 1\textsuperscript{o} or 2\textsuperscript{o} degree relatives with any HNPCC related tumor
Familial Colorectal Cancer Type X

- Families meet Amsterdam I criteria but,
- CRC is negative for MSI
- No increased risk of extracolonic ca
- No known gene mutation
Familial Colorectal Cancer Type X

Implications

• Screen for colorectal cancer
• Relax screening for extracolon cancers
Strategies to Identify the Lynch Syndrome Among Patients with Colorectal Cancer

Ladabaum et al.
Aim

Use decision analysis to explore economic consequences of competing strategies of identifying Lynch syndrome beginning with newly diagnosed cases of CRC
Methods

Strategies

• Clinical then genetic testing
• Tumor testing the germline
• Germline testing
Table 1. Base-Case Results*

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IHC = immunohistochemistry; MSI = microsatellite instability.
* Strategies are shown in order of increasing effectiveness. Total cohort size of 100,000 persons with a ratio of 8 relatives per proband, a germline testing acceptance rate of 0.52 by relatives, and the assumption that clinical criteria are determined for all probands. Cancer cases and deaths include those in probands and those in relatives with and without mutations associated with the Lynch syndrome. Results account for incomplete acceptance of germline testing, screening, and prophylactic surgery. For the clinical algorithm strategies that include IHC, IHC was reserved for those whose predicted probability of carrying a mutation was >5%.
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#### Tumor-testing strategies
- IHC
- IHC with \( \text{BRAF} \) testing
- MSI
- MSI plus IHC
- MSI plus IHC with \( \text{BRAF} \) testing

#### Up-front germline testing

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<td>Heart transplant</td>
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Conclusion

- CRC undergo routine tumor testing so MD does not order but must notify
- Best strategy IHC if no protein then BRAF
- Screening up to 70 yo seems reasonable
- Future develop may change analysis
  - Cost of germline testing, testing other member, interventions not as good
Familial Adenomatous Polyposis
Familial Adenomatous Polyposis

- Autosomal dominant disease
- Mutation of APC gene
- Hundreds of adenomas in colorectum
- Presence/absence extracolonic lesions
- Colorectal cancer inevitable
Cause of FAP

- Mutation of APC gene (Adenomatous Polyposis Coli)
- Located chromosome 5q 21
- Discovered 1991
Clinical Course

Puberty - polyps appear
15 y.o. – onset of polyps
33 y.o. - symptoms appear
36 y.o. – age of diagnosis
39 y.o. – age of colorectal cancer dx
42 y.o. - death from colorectal cancer
Treatment

- Proctocolectomy/ ileostomy
- Proctocolectomy/ ileoanal pull through
- Colectomy/ ileorectal anastomosis
APC GENE

CLASSIC FAP

5’ codons 0 158

1596 2843 3’

RNA

PROTEIN
APC GENE

CLASSIC FAP

5' codons 0 158 1596 2843 3'

RNA

PROTEIN
Attenuated FAP

- 5’ and 3’ APC gene mutations
- 6% of FAP pedigrees
- Oligopolyposis (<100 adenomas),
- Polyps right-sided
- Heterogeneous phenotype
- Later CRC (51 vs 39 y.o.)
Screening

• At-risk persons (1st degree relatives)
• Sigmoidoscopy
  q yr starting age 12,
  q 2 yrs after age 25,
  q 3 yrs after age 35,
  average risk guidelines after age 50
Screening: APC Gene Testing

• Gene test for mutation of APC gene
• Start at-risk persons age 10-12
• Pretest genetic counseling/ consent
• Test affected pedigree member first
APC Gene Testing - At Risk

APC mutation
APC Gene Test Result

- Positive - FAP - sigmoid. yearly
- Negative - No FAP - sigmoid. age 25
MYH Associated Polyposis (MAP)
MYH Associated Polyposis

- Discovered in 2003
- Caused by mutation MYH (MutYH) gene
- Polyposis (> 100 polyps)
- Oligopolyposis (< 100 polyps)
- Autosomal recessive condition
MAP

- Polyposis (> 100 polyps) - 0.4%

- Oligopolyposis (5-100 polyps) - 4% to 33%
MYH Gene

- Base excision gene
- Two deleterious mutations
  - Y165C and G382D
- Prevents mutations in DNA
- Fixes damaged base pairs
- Damaged by oxidative stress
G=C
Oxidative Damage

\[
G=C \rightarrow
\]
Oxidative Damage

\[ G=C \rightarrow G^{*}=C \]
Oxidative Damage

\[ G=C \rightarrow G^*=C \rightarrow G^*=A \]
Oxidative Damage

\[ G=C \rightarrow G^*=C \rightarrow G^*=A \rightarrow T=A \]
Oxidative Damage

G=C → G*=C → G*=A → T=A

MYH
Oxidative Damage

\[ \text{G=C} \rightarrow \text{G*=C} \]

MYH
Oxidative Damage

\[
G = C \rightarrow G^{*} = C \rightarrow G = C 
\]

MYH
MYH Gene

Polyposis
CRC risk (carrier)
CRC risk (carrier)
Normal risk
MYH Management

- Biallelic mutations - like FAP or AFAP
- Monoallelic mutation - colonoscopy at 40 yr q 10 yrs (q 5 yrs).
Family A

- crc 59
- gaca36
- ca 47
- brca 36
- crc 40
- ut 40
- bldca 73
- p 58
- crc 55
- crc 36
- 35
- p 33
- 31

- crc 25

- crc 45,52
- ov/ut 44
Family B

crc 83 yr

53 yr sig resection

20 yr
>100 adenomas

2 yr
1 mo
Family C

74 yo
nl colon 70 yo

38 yo
40 adenomas

36 yo
50 adenomas

33 yo

11 yo
12 yo
Family C

- 74yo polyposis
- 38 yo
  - 40 adenomas
- 36 yo
  - 50 adenomas
- 33 yo
- 11 yo
- 12 yo
Summary
Summary

• Lynch syndrome
  – colonoscopic screening
  – MSI/IHC testing, MMR gene testing
Summary

• Lynch syndrome
  – colonoscopic screening
  – MSI/IHC testing, MMR gene testing
• Familial Colorectal Cancer Type X
  – Amsterdam I, MSI stable
Summary

• Lynch syndrome
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• Familial Colorectal Cancer Type X
  – Amsterdam I, MSI stable

• FAP/AFAP
  – APC gene testing
  – sigmoid/colonoscopy screening
Summary

- MAP
  - MYH gene testing
1. What is differential dx?
1. What is differential dx?
Oligopolyposis

64 yo  72 yo  d68 MI  78 yo  2 polyps  76 yo  Lung ca  d58 MI

49 yr  42 yo  46 yo

2 CRCs, 10 adenomas

17 yo
1. What is differential dx? Oligopolyposis
2. What genetic tests?

- 49 yr
- 2 CRCs, 10 adenomas
- 17 yo
- 78 yo
- 2 polyps

- 42 yo

- 76 yo
- Lung ca

- 46 yo

- 72 yo

- 64 yo

- d 68 MI

- d 90s

- d 78s

- d 80s

- d 58 MI
1. **What is differential dx?**
   - Oligopolyposis

2. **What genetic tests?**
   - APC and MYH

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   - d 90s

Genetic findings:
- MYH +/+
- 25% normal
- 50% monoallelic
- 25% biallelic
1. What is differential dx?
   Oligopolyposis

2. What genetic tests?
   APC and MYH

3. Risk to relatives?

   - 17 yo
   - 49 yr
     - 2 CRCs, 10 adenomas
     - MYH +/-

   - 42 yo
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     - 2 polyps
     - Lung ca
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   25% normal
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Summary

• HNPCC
  – colonoscopic screening
  – MSI/IHC testing, MMR gene testing
• FAP/AFAP
  – APC gene testing
  – sigmoid/colonoscopy screening
• MAP
  – MYH gene testing
Objectives

• Name the forms of hereditary colorectal cancer

• Understand the genetic tests which screen and diagnosis hereditary forms of colorectal cancer
Topics

• Didactics

• Cases
Topics

- Didactics
- Cases
Topics

• Didactics

• Cases
Methods
Methods

• Decision analysis model
  – Compare germline or tumor testing vs. no testing

• Events modeled
  – 1st colorectal, endometrial, ovarian, cancer
  – Metachronous CRC, screen/Rx complications
  – Death from cancer and other causes
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| Tumor-testing strategies       |
| IHC                            |
| IHC with **BRAF** testing      |
| MSI                            |
| MSI plus IHC                   |
| MSI plus IHC with **BRAF** testing |

IHC = immunohistochemistry; MSI = microsatellite instability.

* Strategies are shown in order of increasing effectiveness. Total cohort size of 100,000 persons with a ratio of 8 relatives per proband, a germline testing acceptance rate of 0.52 by relatives, and the assumption that clinical criteria are determined for all probands. Cancer cases and deaths include those in probands and those in relatives with and without mutations associated with the Lynch syndrome. Results account for incomplete acceptance of germline testing, screening, and prophylactic surgery. For the clinical algorithm strategies that include IHC, IHC was reserved for those whose predicted probability of carrying a mutation was ≥5%.

† Strategies that were dominated by simple or extended dominance are excluded.