Hereditary Colon Cancer Syndromes: Diagnosis, Screening and Management

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Learning Objectives

- Patterns of inheritance of hereditary cancer risk
- Goals of genetic counseling and testing for cancer risk
- Clinical and Biological Aspects of Hereditary Polyposis Syndromes and Lynch Syndrome
- Multigene Panels for Hereditary Cancer Susceptibility testing
Opportunities to Increase Cancer Survival

- Genetic testing for cancer risk susceptibility
- Increased focus on early detection and prevention
- Tumor Profiling and Targeted Therapies
The Development of Hereditary Cancer

**Nonhereditary**
- 2 normal genes
- 1 damaged gene
- 1 normal gene
- Loss of normal gene

**Hereditary**
- Mother or Father
- 1 damaged gene
- 1 normal gene

**Loss of normal gene**
Most Cancer Susceptibility Genes Are Dominant With Incomplete Penetrance

- Penetrance is often incomplete
- May appear to “skip” generations
- Individuals inherit altered cancer susceptibility gene, not cancer
Age-Specific Penetrance

Percentage of individuals with an altered disease gene who develop the disease

Affected with colorectal cancer (%)
Hereditary Susceptibility to Cancer

- Who to test for genetic susceptibility?

- What are the risks of cancer associated with known genetic mutations?

- What can be done to prevent cancer in unaffected carriers?
## Colorectal cancer risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Lifetime risk</th>
<th>Screening colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average risk</td>
<td>4-5%</td>
<td>Start at age 50, every 10 years if normal</td>
</tr>
<tr>
<td>Obesity</td>
<td>~6%</td>
<td>Start at age 50, every 10 years if normal</td>
</tr>
<tr>
<td>Diabetes</td>
<td>~6%</td>
<td>Start at age 50, every 10 years if normal</td>
</tr>
<tr>
<td>Red/processed meat</td>
<td>~6%</td>
<td>Start at age 50, every 10 years if normal</td>
</tr>
<tr>
<td>Western diet</td>
<td>~6%</td>
<td>Start at age 50, every 10 years if normal</td>
</tr>
<tr>
<td>Alcohol</td>
<td>~6%</td>
<td>Start at age 50, every 10 years if normal</td>
</tr>
<tr>
<td>Smoking</td>
<td>~6%</td>
<td>Start at age 50, every 10 years if normal</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>50%</td>
<td>Start at age 20-30, every 1-2 y</td>
</tr>
<tr>
<td>Polyposis syndromes</td>
<td>Varies with syndrome</td>
<td>Follow guidelines</td>
</tr>
<tr>
<td>UC/Crohn’s</td>
<td>20-40%</td>
<td>Start 8-10 y after diagnosis</td>
</tr>
<tr>
<td>Family history</td>
<td>10-15%</td>
<td>Start at 40 or 10 years younger than family member at diagnosis, every 5 y</td>
</tr>
<tr>
<td>Personal history of cancer or polyps (adenoma)</td>
<td>20%</td>
<td>Follow guidelines</td>
</tr>
</tbody>
</table>
# Colorectal cancer risk by genetic syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Population frequency</th>
<th>Absolute risk of CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome</td>
<td>MLH1/MSH2</td>
<td>1:300-1:700</td>
<td>50% by age 75</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MSH6/PMS2</td>
<td>1:300-1:700</td>
<td>20% by age 75</td>
</tr>
<tr>
<td>FAP</td>
<td>APC</td>
<td>1:7,000-30,000</td>
<td>90% by age 40</td>
</tr>
<tr>
<td>AFAP</td>
<td>APC</td>
<td>1:7,000-30,000</td>
<td>70% by age 80</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
<td>1:8000-1:200,000</td>
<td>40% by age 70</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>SMAD4/BMPR1A</td>
<td>1:100,000</td>
<td>20-70% by age 60</td>
</tr>
<tr>
<td>MAP*</td>
<td>MUTYH (biallelic)</td>
<td>&lt;0.02%</td>
<td>50-80%</td>
</tr>
</tbody>
</table>
Colorectal Multistep Carcinogenesis

Chromosomal Instability

Normal Colorectal Epithelium → Early Adenoma → Intermediate Adenoma → Advanced Adenoma → Colorectal Carcinoma → Invasive Carcinoma → Metastatic Carcinoma

Microsatellite Instability

hMSH2 → hMLH1 → MMR → APC → TGFBRII → MSH3 → IGFII → MSH6 → BAX → PTEN → ?? → ??
Categories of colorectal cancer (CRC)

- **Sporadic** (~65%)
- **Familial** (~30%)
- **Hereditary Nonpolyposis Colorectal Cancer (Lynch)** (5%)
- **Familial Adenomatous Polyposis (FAP)** (1%)
- **Rare CRC syndromes** (<0.1%)
- **Unknown gene**
Familial adenomatous polyposis (FAP)

- Autosomal dominant, 90-100% cancer penetrance
- Accounts for <1% of colorectal cancer
- Desmoid tumors, congenital hypertrophy of retinal pigment epithelium (CHRPE); nonepithelial benign tumors (osteomas, epidermal cysts, dental abnormalities = Gardners sx)
- Thyroid/brain tumors, hepatoblastoma
- Knudson’s second-hit hypothesis => adenomas develop
  - Additional mutations for cancer formation
  - >1000 mutations known; 25% de novo

*Kinzler KW & Vogelstein B. Cell 1996;87:159.; De la Chapelle A. Nat Rev 2004;4:469*
Attenuated FAP

- Mutations at the 3´ and 5´ end of APC and missense mutations
- 10-20 adenomas, <100
- For FAP: Screening with colonoscopies/flex sigs from 10-15 years, q1-2y; offer colectomy once polyps arise
- Testing for FAP/AFAP: (NCCN)
  - Test all with >20 adenomas
  - Test if 10-20 adenomas + desmoid tumors/other features of FAP
Clinical Features of FAP

- Estimated penetrance for adenomas >90%
- Risk of extracolonic tumors (upper GI, desmoid, osteoma, thyroid, brain, other)
- CHRPE may be present
- Untreated polyposis leads to 100% risk of cancer
FAP: Age and Development of Adenomas and CRC

% of patients with neoplasia

Age

FAP

Adenomas
CRC

General population

Bussey HJR. Familial Polyposis Coli, 1975
Some FAP Manifestations Correlate With Specific $APC$ Gene Regions

- Attenuated FAP
- Classic FAP
- CHRPE

123456789101112131415
FAP, Management

- Genetic testing
- Colonic screening
  - Annual sigmoidoscopy
  - Start at age 10 to 12 years
  - Colonoscopy for AAPC
- Preventative Surgery
- Chemoprevention
MUTYH polyposis

- Base excision repair gene (oxidative damage)
- Recessive (homozygous)
- 1-2% carry a heterozygous mutation
  - Y179C and G396D
- Screen with colonoscopies every 1-2 years from 25-30
- Extracolonic cancers
- Increased cumulative risk in heterozygous individuals
  - 7.2% in males by 70; 5.6% in females by 70
  - If fhx with FDR it was 12.5% and 10%

Hamartomatous polyposis syndromes

- **Peutz-Jeghers syndrome**
  - *LKB1/STK11* (up to 94% of individuals)
  - Melanocytic macules on lips/buccal area, GI polyps
  - Breast cancer, ovarian cancer, GI cancers (lifetime risk 38-66%)

- **Juvenile polyposis**
  - *SMAD4* (15-60%), *BMPR1A* (25-40%), *ALK1* (assoc with HHT)
  - CRC (lifetime risk 39%)
  - Hereditary hemorrhagic telangiectasia

- **Cowden disease/Bannayan-Ruvalcaba-Riley syndrome**
  - *PTEN* mutations (60-85%)
  - Mucocutaneous manifestations, cerebellar gangliocytoma
  - Breast, thyroid, endometrial, kidney cancers, melanoma
Other high/moderate-risk genes in colorectal cancer

- **High-risk genes**
  - Many studies have focused on familial colorectal cancer type X (FFCX)
    - Meet Amsterdam/Bethesda criteria but no Lynch syndrome
  - **GREM-1** (Jaeger et al. Nature Gen 2012)
  - **POLE/POLD-1** (Palles et al. Nature Gen 2013)
  - **FAN-1** (Segui N Gastroenterology 2015)
  - **TP53** (Yurgelun et al. JAMA Onc 2015)
  - **RPS20** (Nieminen TT Gastroenterology 2014)

- **Moderate risk genes**
  - **APC I1307K** (Azhkenazi Jewish) (Boursi et al. Eur J Ca 2013)
  - **BLM heterozygotes** (de Voer et al. Sci Rep 2015)
  - **CHEK2** (Xiang HP Eur J Ca 2011)
  - **GALNT12** (Gouda PNAS 2009)
  - **MUTYH heterozygotes** (Win et al. Gastro 2014)
  - **ATM** (Thompson D JNCI 2005)

- **NCCN recommendation**
  - Colonoscopy at age 40 or 10 years younger than FDR at diagnosis, every 5 years
The history of Lynch syndrome:

Warthin A. Archives of Int Med. 1913; XII(5):546-555.

Clinical Features of Lynch Syndrome

- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates (2/3rds)
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, brain, sebaceous skin tumors
- Autosomal pattern of inheritance
Contribution of Gene Mutations to LS Families

- MSH2: ~30%
- MLH1: ~30%
- PMS2: (rare)
- MSH6: (rare)
- Unknown: ~30%
- Sporadic
- Familial
- HNPCC
- Rare CRC syndromes
- FAP
- MLH1: ~30%

Rare CRC syndromes

Familial

Unknown

~30%

Sporadic

MSH2

~30%

MLH1

~30%

MSH6 (rare)

PMS2 (rare)
Amsterdam and Bethesda criteria

- **Amsterdam** (1990/1997)
  - 3: relatives with LS-related cancer
  - 2: generations
  - 1: <50 yo at diagnosis
  - Rule out FAP

- **Bethesda** (1997/2004)
  - CRC < 50
  - Synchronous or metachronous CRC or other LS-tumors
  - MSI-high CRC in individual < 60
  - 1 or more FDR with CRC or a LS-tumor < 50
  - CRC or a LS-tumor in 2 FDR or SDR at any age
How to identify persons who may have LS?

- Family history (Amsterdam criteria)
- Clinical criteria for MSI testing in persons with CRC, EC (Bethesda guidelines)
- Tumor testing in persons with CRC, EC (Universal IHC)
- General population screening?
Mismatch Repair Genes

New DNA strand

Template DNA
Model of Microsatellite Instability

\[
\text{C-A} \\
\text{-G-T-G-T-G-T-G-T-G-T-G-T-G-T-}
\]

If unrepaired on template strand → Deletion
primer strand → Insertion

Assay for MSI

\[
(\text{CA})_n \\
(\text{GT})_n \\
\text{PCR}
\]

NL1  NL2  MSI

MSI-H defined as instability at \( \geq 2 \) of 5 or \( \geq 30\% \) of loci
Microsatellite markers and detection of MSI
Immunohistochemistry

- Identify MMR proteins
- Normally present
- If protein is absent, gene is not being expressed (mutation or methylation)
- Helps direct gene testing by predicting likely involved gene
- If abnormal IHC (absent), MSI+

MLH1

MSH2

PMS2

MSH6
Cancer Risks in Lynch Syndrome

Aarnio M et al. *Int J Cancer* 81:217, 1999
## Surveillance Options for LS Mutation Carriers

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Intervention</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer</td>
<td>Colonoscopy</td>
<td>Begin at age 20 – 25, repeat every 1 – 2 years</td>
</tr>
<tr>
<td>Endometrial / Ovarian Cancer</td>
<td>Transvaginal ultrasound, Endometrial aspirate, TAH/BSO</td>
<td>Annually, starting at age 35</td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td>EGD</td>
<td>Begin at age 30 - 35, repeat every 2 – 3 years</td>
</tr>
<tr>
<td>Renal/Ureteral</td>
<td>Urine cytology</td>
<td>Annually, starting at age 30</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>MRI/EGD-US</td>
<td>Per FHx</td>
</tr>
<tr>
<td>Brain</td>
<td>MRI</td>
<td>Per FHx</td>
</tr>
</tbody>
</table>

*NCCN Guidelines 2015*
Colonoscopy Improves Survival of Genetically-Confirmed HNPCC

Survival rates over follow-up time (years):
- Surveillance: 92.2%
- No surveillance: 73.9%
Familial Risk for Common Cancers

Breast Cancer
- TP53, PTEN
- BRCA1
- BRCA2
- ATM, CASP8, CHEK2, PALB2, BRIP1
- Unexplained familial risk
- GWAS SNPs

Colorectal Cancer
- FAP, MYH, other
- Lynch syndrome
- Unexplained familial risk
- GWAS SNPs

Prostate Cancer
- BRCA2
- GWAS SNPs
- Unexplained familial risk

Unexplained familial risk is a major contributor to the risk of developing common cancers.
Cancer Susceptibility Loci

![Graph showing genetic loci and their association with cancer susceptibility. The graph plots relative risk against minor allele frequency. Key loci include TP53, PTEN, BRCA1, BRCA2, STK11, BRIP1, ATM, PALB2, CHEK2, TOX3, MAP3K1, FGFR2, LSP1, AKAP9, and CASP8. The graph illustrates the transition from high-risk alleles in family studies to low-risk alleles in genomewide association studies.]
## Cancer Gene Panels

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>FANCE</td>
<td>PMS2</td>
</tr>
<tr>
<td>ATM</td>
<td>FANCF</td>
<td>PRSS1</td>
</tr>
<tr>
<td>BLM</td>
<td>FANCG</td>
<td>PTCH1</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>FANCI</td>
<td>PTEN</td>
</tr>
<tr>
<td>BRCA1</td>
<td>FANCL</td>
<td>RAD51C</td>
</tr>
<tr>
<td>BRCA2</td>
<td>LIG4</td>
<td>RET</td>
</tr>
<tr>
<td>BRIP1</td>
<td>MEN1</td>
<td>SLX4</td>
</tr>
<tr>
<td>CDH1</td>
<td>MET</td>
<td>SMAD4</td>
</tr>
<tr>
<td>CDK4</td>
<td>MLH1</td>
<td>SPINK1</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>MLH2</td>
<td>STK11</td>
</tr>
<tr>
<td>EPCAM</td>
<td>MSH6</td>
<td>TP53</td>
</tr>
<tr>
<td>FANCA</td>
<td>MUTYH</td>
<td>VHL</td>
</tr>
<tr>
<td>FANCB</td>
<td>NBN</td>
<td></td>
</tr>
<tr>
<td>FANCC</td>
<td>PALB2</td>
<td></td>
</tr>
<tr>
<td>FANCD2</td>
<td>PALLD</td>
<td></td>
</tr>
</tbody>
</table>
Multiple Gene Panel Test Results

- 36 of 361 women without $B1/2$ (10%) carried a potentially pathogenic mutation
  
  ATM, BLM1, CDH1, CHEK2, MLH1, MSH2, MSH6, PMS2, MUTYH, NBN, PRSS1, SLX4, RAD51C, PALB2, BRIP1

- Participants notified of significant results
  
  11/14 from pilot set followed-up, confirmed, counseled

- Variants of Uncertain Significance (VUS) were common
  
  40% of patients (0.7 per patient)

Kurian, Ford et al. Journal of Clinical Oncology 2014
Ford, Montreal BRCA Conference 2014
Multigene Panel: Clinical Case 1

- d. 70y heart disease
- d. 55y pancreatic cancer @ 55y
- d. late 70s BRCA @ 70s
- d. 50s MI
- d. 85y dementia

- 75y no cause
- d. 60y heart disease
- 70y basal cell cancer
- 55y ovarian cancer @ 55y
- 50y BRCA @ 70y

- 40y
- 52y BRCA @ 35y triple neg
- Endometrial CA @ 44y
- TP53 neg/BRCA1/2 B neg

- 50y no cause

- 57y
- 50s
- 50s
- 50s

- 21y
- d. 10y Neuroblastoma
- 34y
- 30y
Multigene Panel: Case 1

- 45 yo woman
- Triple-negative breast cancer at 35, BRCA1/2 testing negative
- Found by panel study to be MLH1 positive (Hereditary colon cancer syndrome)
- Colonoscopy performed: Positive (pre-cancerous polyps found and removed)
Prognostic implication of dMMR in stage 2-3

Fig 2. Forest plots of hazard ratios (HRs) of overall survival in studies of all stage II-III colorectal cancer associated with microsatellite instability. Cohort of patients with (*) stage II, (**) stage III, or (***) stage IV colorectal cancer.

Popat et al. JCO 2005.
Prognosis in Lynch syndrome vs. MLH1-hm

Figure 1  Overall survival (months) in all stages in patients with Lynch syndrome–associated colorectal cancer (CRC) and sporadic inactivation of MLH1 by hypermethylation CRC.

Figure 2  Cancer-specific survival (months) in all stages in patients with Lynch syndrome–associated colorectal cancer (CRC) and sporadic inactivation of MLH1 by hypermethylation CRC.

<table>
<thead>
<tr>
<th>Cancer-specific survival (months)</th>
<th>LS</th>
<th>MLH1-hm</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>1.07 (0.08–13.6)</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>NR</td>
<td>1.11 (0.22–5.64)</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>23.5</td>
<td>17</td>
<td>2.07 (0.32–13.5)</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>1.33 (0.46–3.83)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Predictive implication of dMMR in stage 2-3

Disease-free survival by MMR Status, 5-FU/LV vs. obs

Treated (N=512)

Untreated (N=515)

Pooled data from 5 adjuvant trials in CRC

Sargent et al. JCO 2010;28:3219.
Predictive implication of dMMR in stage 2

Overall Survival By treatment; Stage II dMMR Patients

5 yr OS

Untreated  93%
Treated    75%

HR: 3.15 (1.07-9.29); p=0.03

P-value = 0.014 for treatment by MMR status interaction

Sargent et al. JCO 2010;28:3219.
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


Table 2. Objective Responses According to RECIST Criteria.

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N = 10)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N = 18)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)†</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%)</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
<td>40 (12–74)</td>
<td>0 (0–19)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — %</td>
<td>90 (55–100)</td>
<td>11 (1–35)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
<td>Not reached</td>
<td>NA‡</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
<td>28 (13–35)</td>
<td>NA‡</td>
<td>12 (10–13)</td>
</tr>
</tbody>
</table>
Genomic Profiling: What to Expect

Phase 2 trial with pembrolizumab

- 41 patients in 3 cohorts
  - A: dMMR CRC
  - B: pMMR CRC
  - C: dMMR non-CRC

- Inclusion: Metastatic disease, CRC failed 2 lines, non-CRC failed 1 line; MSI-high (later amended to include dMMR by IHC)

- Pembrolizumab 10 mg/kg q2w iv

- Primary endpoints: Immune-related ORR and irPFS at 20 weeks

Phase 2 trial with pembrolizumab

B Radiographic Response

Change from Baseline in the Sum of Longest Diameters (%)

-100
-50
0
50
100

Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer

20% increase (progressive disease)
30% decrease (partial response)

Figure 1. Clinical Responses to Pembrolizumab Treatment.

Le DT. et al. NEJM 2015.
Colorectal Cancer Genomics

15% MIN (MSI+)
(Microsatellite Instability)

Lynch Sx
Germline Mutation
MMR genes
MLH1, MSH2, MSH6 & PMS2

13% Sporadic MSI(+)
• Epigenetic silencing of
  MLH1 by hypermethylation
  of its promoter region

85% CIN
(Chromosome Instability)

<1% FAP
Germline Mutation
APC

85% Sporadic
Acquired
APC, p53, DCC, kras, LOH,...

Courtesy of Dr. Richard M. Goldberg
Summary

- GI cancer genetics are complicated
- Cancer genetics have taught us about tumor genomics
  - FAP and APC mutations
  - Lynch syndrome and MMR mutations
- Universal screening for Lynch syndrome
  - Immunohistochemistry or MSI testing by PCR
  - Identify families with Lynch syndrome to prevent cancer
  - Affect management of stage 2 and 4 cancer (PD-1)
- Multi-gene panel testing
  - Rapidly acquiring knowledge about other mutations