FAP and Lynch Syndrome (HNPCC)
Surveillance and chemoprevention for colon and extracolonic cancers

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FAP and Lynch Syndrome (HNPCC)
Surveillance and chemoprevention for colon and extracolonic cancers

- Prevalence
- Clinical features
- When should we test?
- Guidelines for management of colonic neoplasia
  - Surveillance colonoscopy, surgery, chemoprevention
- Screening and Surveillance for extracolonic tumors
Prevalence of Hereditary Colon Cancer Syndromes

Sporadic (65%–85%)

Familial (10%–30%)

Rare CRC Syndromes
- MYH Polyposis
- PJS, Cowden’s, JPC

Familial Adenomatous Polyposis (FAP) (<1%)

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) (2-3%)

Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996
Prevalence of Hereditary Colon Cancer Syndromes

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- Rare CRC Syndromes
  - MYH Polyposis
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Familial Adenomatous Polyposis (FAP)
Clinical Features of FAP

- Rare- 3/100,000- 1/13,000
- Hundreds to thousands of colonic adenomas
- Average age of polyp occurrence: 16 years
- 100% risk of colon cancer, average age: 39 years, youngest 9
- Others Duodenum 5-10%, thyroid 1%, Desmoids, Gastric (fundic, adenoma)
- Autosomal Dominant; APC (5q)
FAP: Age and Development of Adenomas and CRC

% of Patients with Neoplasia

General population

FAP

Adenomas
CRC

Age

Bussey HJR. *Familial Polyposis Coli*, 1975
Location Matters

- Later onset (CRC ~age 50)
- Fewer colonic adenomas
- Lower penetrance CRC

5' 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 MCR

Classic FAP
Attenuated FAP
Location Matters

- Osteomas
- Fibromas
- Epidermoid Cysts

MCR

“Gardner’s”
When to consider FAP Gene Testing

- Any individual with more than 100 adenomas
- First degree relatives of known FAP patients
Clinical Approach to Genetic Testing

- Person known to have FAP phenotype tested first
- If mutation found, testing can be done in family members with near 100% accuracy
- If no mutation found, all family members should be clinically screened
- Genetic counseling important
- Consider referral for genetic diagnosis

Clinical Management - Classic FAP

- Lower endoscopy annually ~ age 10 to 40 years
- Upper GI screening when colonic adenomas appear (side viewing) and every 3-5 years if negative
- Appropriately time total proctocolectomy
- Surveillance of ileal pouch
- Screening for thyroid cancer
- High clinical suspicion for desmoids
- Consider use of Sulindac or Celecoxib to assist treatment planning
Clinical Management- Attenuated FAP

- Colonoscopy 1-2 years, beginning at age 20-25 years depending on the family history
- Complete polypectomy or colectomy
  - Subtotal or Total with ongoing surveillance
- Rest as for classic FAP
Diagnosis and Management of Hereditary Colon Cancer Syndromes

- Identify High Risk Families Clinically
  - Adenomatous Polyposis Syndromes- APC, MYH
  - HNPCC
  - Hamartomatous Syndromes
- Genetic Counseling/Testing when possible
- Screening/Surveillance- Gene carriers/at risk members
- Management
MAP can mimic FAP

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MYH Associated Polyposis < 1%?

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MAP
- Polyposis Syndrome
- Autosomal Recessive
- Bi-allelic Germ Line Mutation in MYH
- Base Excision Repair Gene
- BER repairs oxidative DNA damage
Clinical Features and Management of MYH Polyposis

- Autosomal Recessive
- G-T Transversions in APC
- Scores to hundreds (< 500) of colonic adenomas
- 10% APC negative FAP
- 15-30% Multiple adenomas
- Management like FAP
Clinical Features of HNPCC

- Autosomal dominant
- Average age of CRC - 44 yrs
- Only few adenomas
- Cancers and adenomas favor proximal colon location
- Other cancers
- Due to germline mutation in one of MMR genes
HNPCC Results From Failure of Mismatch Repair (MMR) Genes

Base pair mismatch

Normal DNA repair

Defective DNA repair (MMR+)

T C T A C
A G C T G

T C G A C
A G C T G

T C T A C
A G C T G

T C T A C
A G A T G
Incidence of CRC in Lynch Syndrome vs Sporadic

Voskuil, Int. J. Cancer, 1997
Cancer Risks in HNPCC

% with cancer

Colorectal 78%  
Endometrial 43%  
Stomach 19%  
Biliary tract 18%  
Urinary tract 10%  
Ovarian 9%

Gene Testing in Families that Meet Amsterdam Criteria

- Sporadic
  - Rare CRC syndromes
  - FAP

- Familial
  - Unknown ~30%
  - MSH2 ~30%
  - MLH1 ~30%
  - PMS1 (rare)
  - PMS2 (rare)
  - MSH6 (rare?)

Attenuated HNPCC - MSH6 Mutations

- 20 families with MSH6 mutations - 146 carriers
- Cancers occur later than MSH2/MLH1
  - CRC ≈ 10 years later (56)
  - Endometrial ≈ 5 years later (54)
- Cumulative risk by age 70 ≈ MSH2/MLH1

Hendricks et al Gastroenterology 2004
DNA MMR and CRC

Microsatellite Instability - DNA Mismatch Repair
hMLH6 - Later onset of cancers, higher endometrial risk

Normal Epithelium  Microsatellite Mutant Foci  Early Adenoma  Advanced Adenoma  Adenocarcinoma

Microsatellite Unstable  Diploid  Lymphocyte Infiltration

When to consider HNPCC gene testing

- **Amsterdam criteria** - 3 Lynch cancers, 2 generations, 1 under age 50
- **Bethesda criteria** for MSI testing of tumor then do gene testing if positive
  - Any CRC under age 50
  - Anyone with CRC with Lynch histology under age 60
  - Anyone with 2 Lynch cancers
Screening/Surveillance in HNPCC

- Genetic testing (MSI, then mutation finding), start with index case
- Colonoscopy, age 25 years, or 10 years younger than earliest diagnosis, repeat every 1-2 years
- Appropriately timed colectomy
- Other tumor screening
  - Endometrial, ovarian, gastric, biliary, small bowel, urinary tract
- Chemoprevention - NSAIDs?
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- Prevalence - rare - 3-5% of all CRC but may be underestimating
- Clinical features - family history
  - polyposis vs cancer phenotype
- When should we test - based on phenotype and FH
- Screening, Surveillance and Mgmt of colonic and extracolonic tumors
  - Specific to each syndrome