Colorectal Cancer Screening

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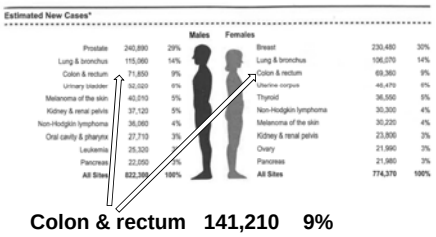
Estimated new cancer cases U.S. 2011

Estimated New Cases



Colon & rectum 141,210 9%

CA Cancer J Clin volume 61; number 4; july/august 2011

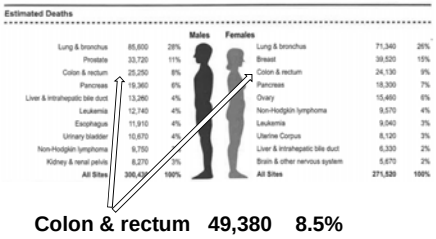
Colorectal Cancer Screening

Why?

Primary Goal is to Prevent Deaths from Colon Cancer

Estimated cancer deaths U.S. 2011

Estimated Deaths



Colon & rectum 49,380 8.5%

CA Cancer J Clin volume 61; number 4; july/august 2011

Colorectal Cancer Prevention

- Most cancers develop from adenomatous polyps
- Progression takes ~10 years
- Screening and polyp removal reduces risk of developing CRC by ~90%
  - Cost effectiveness of CRC screening is consistent with other preventive measures

Colorectal Cancer Survival Rates

Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 2001-2007, All Races, Both Sexes

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localized (confined to primary site)	39	90.1
Regional (spread to regional lymphnodes)	37	69.2
Distant (cancer has metastasized)	20	11.7
Unknown (unstaged)	5	33.3

Data from: Surveillance, Epidemiology, and End Results (SEER) Program, 2002-2006. Available online at http://seer.cancer.gov.

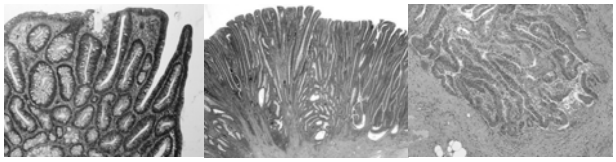
Colorectal Cancer: Early detection

- Early detection associated with improved survival rates
- 5 year survival is ~90% for early stage CRC

Colon Polyps

- Two thirds of polyps are adenomas
- Adenomas are found in ~25% of colonoscopies performed in people age 50 and in ~45% of people age 70
- Risk of CRC increases with adenoma size, number, villous histology

Polyp Histology



Tubular adenoma

Villous adenoma

Colon cancer

Colorectal Cancer Screening

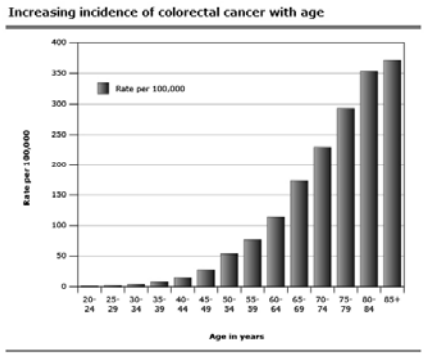
Who?

- **Men and women**
- **Average person has a ~5% lifetime risk of developing CRC - 90% of these occur in people > 50 years old**
- **Begin at age 50 for average risk**

The Downside of CRC Screening Effectiveness

- **Only about half of people 50 years or older undergo screening**
- **Only 4/10 cancers are detected at an early stage**
- **Lack of public or professional awareness**
- **Financial barriers**

Age specific incidence of colorectal cancer



Data from: Surveillance, Epidemiology, and End Results (SEER) Program, 2002-2006. Available online at http://seer.cancer.gov.

Colorectal Cancer Screening

Who?

- **Increased risk groups begin screening before age 50 and/or are screened more often**
- **Personal history of CRC or adenomatous polyps**
- **Personal history of IBD (UC or CD)**
- **Family history of CRC or polyps (especially first degree relative, multiple relatives, age 60 or younger**
- **Family history of hereditary CRC syndrome**

How? CRC Screening for Average Risk Individuals

- **Begin at age 50 for average risk individuals**
- **Colorectal cancer prevention should be the primary goal**

Consensus Guideline 2008: ACS, US Multi-society Task Force on Colorectal Cancer, American College of Radiology

Primary Care Physician Practices

- **99% of physicians recommend CRC screening to patients (majority colonoscopy)**
- **Only 61% reported that their practice had implemented guidelines to ensure that eligible adults were offered screening**
- **Only 30% reported use of any reminder system (eg chart flags or computer prompts)**
- **Only 12% reported receiving a report about CRC screening rates for their patients**
- **FOBT performance issues (in-office testing, difficulty with tracking test completion)**

Cancer Screening in the US, 2011. CA Cancer J Clin 2011; 61: 8-30.

Tests that find polyps and cancer

- **Flexible sigmoidoscopy every 5 years**
- **Colonoscopy every 10 years**
- **Double-contrast barium enema every 5 years**
- **CT colonography (virtual colonoscopy) every 5 years**

Consensus Guideline 2008: ACS, US Multi-society Task Force on Colorectal Cancer, American College of Radiology

Tests that mainly find cancer

- Fecal occult blood test (FOBT) every year
- Fecal immunochemical test (FIT) every year
- Stool DNA test (sDNA) interval uncertain

Consensus Guideline 2008: ACS, US Multi-society Task Force on Colorectal Cancer, American College of Radiology

Screening and Surveillance of Increased Risk Patients

- small rectal hyperplastic polyps --- average risk
- 1-2 small (less than 1 cm) tubular adenomas --- colonoscopy at 5-10 years
- 3-10 adenomas or a large (over 1 cm) adenoma or any adenomas with high grade dysplasia or villous features --- colonoscopy at 3 years

Consensus Guideline 2008: ACS, US Multi-society Task Force on Colorectal Cancer, American College of Radiology

CRC Screening Caveats

- For FOBT and FIT use take-home multiple sample method NOT DRE and stool test [misses >90% of colon abnormalities]
- The best test is the one that the patient will take
- Among all guidelines, there is least consensus on the role of CT colonography and stool DNA testing
- Waning role of barium enema

2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

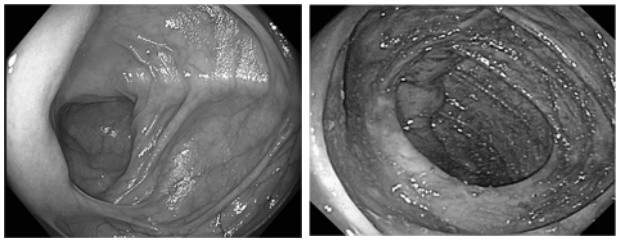
- Cancer PREVENTION tests preferred over cancer DETECTION tests
- Colonoscopy is the preferred CRC prevention test
- Colonoscopy every 10 years beginning at age 50 is preferred strategy; alternatives for patients who decline colonoscopy are flexible sigmoidoscopy or CT colonography

2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

- Screening for African-American persons should begin earlier -- begin at age 45 because of high incidence of CRC and a greater prevalence of right-sided polyps and cancers in this population
- New recommendations for bowel preparation to enhance quality of the exam (split dosing)

2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

- CT colonography performed every 5 years is an alternative for patients who decline colonoscopy
- Barium enema is not recommended for CRC screening/prevention
- Fecal testing is a cancer DETECTION test, not a PREVENTION test; fecal immunohistochemical testing (FIT) replaces the older guaiac-based fecal occult blood test (FOBT)
- Screening recommendations related to family history are modified from the 2008 guidelines.



Images provided courtesy of Dr. Douglas Rex of IUPUI.

FIT Test Kit

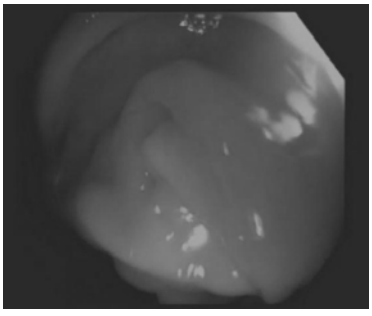
2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

- Key emphasis on QUALITY of colonoscopy
  - Trained examiner
  - Cecal intubation
  - Adenoma detection rate [target 25% in men and 15% in women]
  - Withdrawal times [6 minutes with no biopsies or polypectomies]

2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

- Key emphasis on QUALITY of colonoscopy
  - Polyp removal techniques
  - Piecemeal resection requires close follow up
  - After complete exam and adequate prep, follow screening and surveillance intervals
  - Detection rate is not 100%
  - Risks: perforation rate is <1 in 1,000

Good Withdrawal technique



Video provided courtesy of Dr. Douglas Rex of IUPUI.

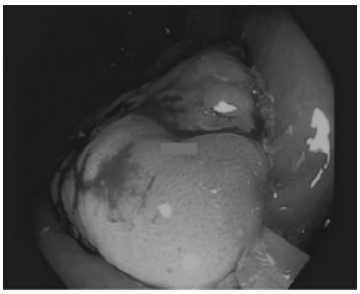
Specific Screening Tests

- Stool DNA
  - Requires submission of an entire bowel movement (on ice) in customized kit
  - Expensive
  - False negatives do occur
  - Significance of "false positives" unknown (positive screen and negative colonoscopy)

Specific Screening Tests

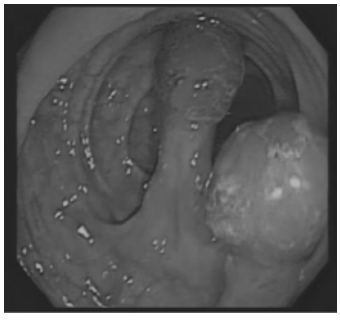
- CT Colonography
  - Multiple CT images
  - Bowel prep required to reduce false positives created by residual stool
  - Colonoscopy recommended for polyps >6 mm
  - Air insufflation required
  - Diagnostic yield for cancers and polyps over 10 mm is similar to colonoscopy
  - Disadvantages include potential miss of flat polyps, radiation exposure, extracolonic findings

Central Injection video



Video provided courtesy of Dr. Douglas Rex of IUPUI.

Final Peduncalated video



Video provided courtesy of Dr. Douglas Rex of IUPUI.

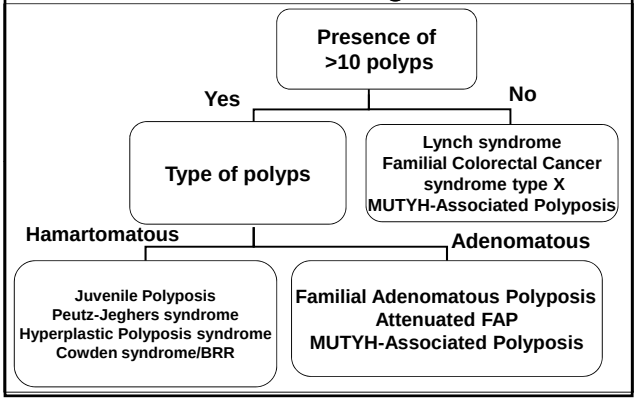
CRC Screening Summary

- Be familiar with and follow consensus recommendations
- Colonoscopy is the preferred screening test
- Any screening is better than no screening
- Screening is not a "one shot" endeavor
- Build system methods to capture the eligible cohort
- Ask about family history

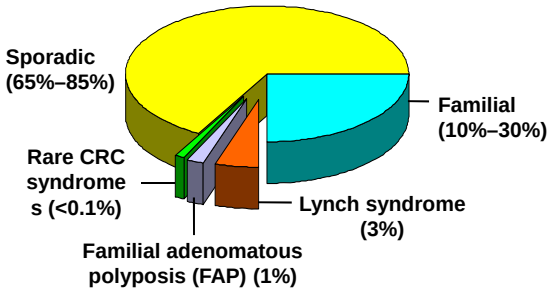
Colon Cancer Screening: Family History Implications

Heather Hampel, M.S., CGC
Professor, Division of Human Genetics
Genetic Counselor
The Ohio State University Comprehensive Center
Arthur G. James Cancer Hospital &
Richard Solove Research Institute

Flowchart for Hereditary Colon Cancer differential diagnosis

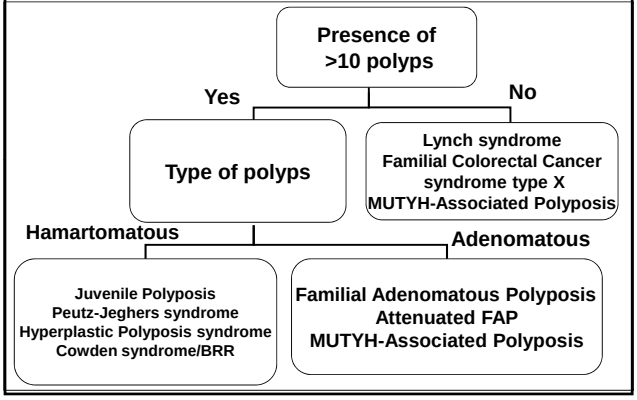


Hereditary susceptibility to CRC



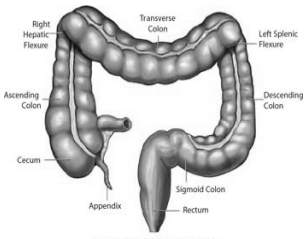
Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996

Flowchart for Hereditary Colon Cancer differential diagnosis



Lynch Syndrome

- **Early but variable age at CRC diagnosis (~45 years)**
- **Tumor site in proximal colon predominates**
- **Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile duct, sebaceous skin tumors**



Anatomy of Large Intestine

Lynch Syndrome Management

Intervention	Recommendation
Colonoscopy	Every 1-2 y beginning at age 20-25 (MLH1 & MSH2), or 30 (MSH6 & PMS2)
Endometrial sampling	Every 1 y beginning at age 30-35
Transvaginal U/S	Every 1 y beginning at age 30-35
Urinalysis with cytology	Every 1-2 y beginning at age 25-35
History & Exam w/ review of systems	Every 1 y beginning at age 21

Lindor N et al. JAMA 2006;296:1507-17. & Vasen HFA et al. J Med Genet 2007;44:353-62.

Lynch Syndrome Cancer Risks (to 70)

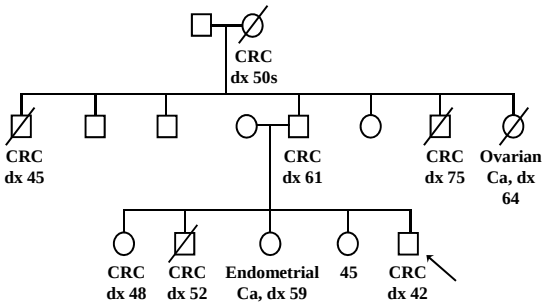
Cancer type	**MLH1& MSH2**	**MSH6**	**PMS2**
Colon cancer (men)	40-80%	10-30%	20%
Colon cancer (women)	40-80%	10-30%	15%
Endometrial cancer	30-60%	15-30%	15%
Stomach	≤13%	≤ 3%	6%
Ovarian	12-24%	1-11%	6%

Lynch Syndrome Prophylactic Surgery Options

- **Options include subtotal colectomy, hysterectomy, and oophorectomy**
- **Subtotal colectomy does not eliminate cancer risk**
- **Hysterectomy eliminates risk of endometrial and ovarian cancer**
- **Expert panels made no recommendation for or against surgery due to unproven efficacy**

Schmeler et al. NEJM 2006;354:261-9.

The Family History Is Key to Diagnosing Lynch Syndrome – or is it?



Bethesda Guidelines

- CRC dx <50
- Synchronous or metachronous CRC, or other HNPCC-associated tumors regardless of age
- CRC with MSI-H histology dx <60
- CRC with ≥1 FDR with an HNPCC-associated tumor, with one cancer dx <50
- CRC with ≥2 FDRs or SDRs with an HNPCC-associated tumor, regardless of age

Umar A, et al. JNCI. 2004;96(4):261-268.

Amsterdam II criteria

- 3 or more relatives with verified HNPCC-associated cancer in family
- 2 more generations
- 1 case a first-degree relative of the other two
- 1 CRC dx <50
- FAP excluded

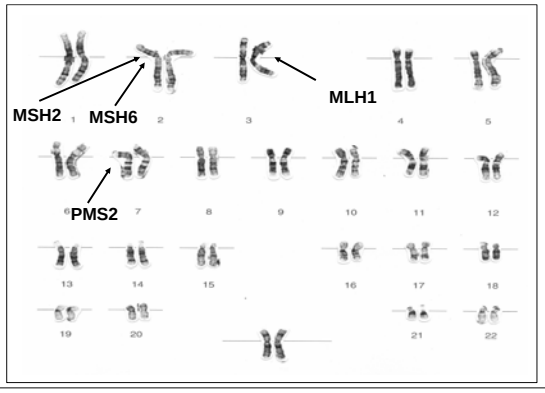
Does not include ovarian, gastric, brain, biliary tract or pancreatic cancer

Vasen HFA et al. *Gastroenterology.* 116:1453, 1999

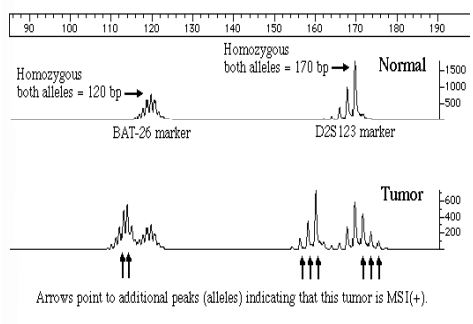
Warning: Family Histories can be Deceiving

- Family size is getting smaller
- Wider use of colonoscopy likely to prevent many colon cancers
- MSH6 & PMS2 have lower cancer risks

Lynch Syndrome Genes



MSI testing on Genotyper

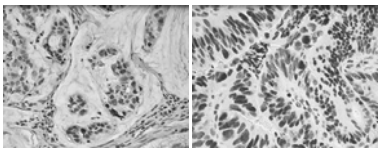


Microsatellite Instability (MSI)

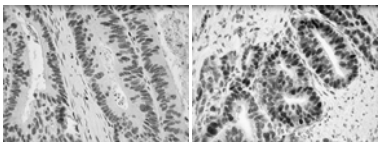
- Repetitive DNA sequences 1- 4 nucleotides (microsatellites) normally found genome
  - Mono: TCGAGG AAAAAAAA GGAGCT
  - Di: TCGAGG CACACACACACA GGAG
- With MMR failure, variability in repeats
- 95% of HNPCC tumors are MSI+
- 10%–15% of sporadic CRCs are MSI+

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

Immunohistochemistry

- Identify MMR proteins
- Normally present
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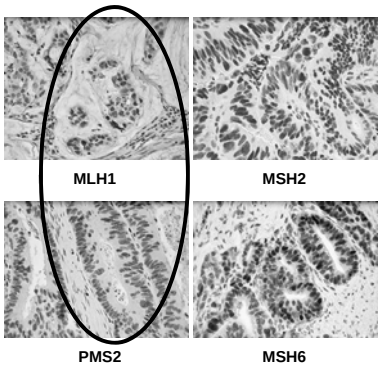
- If abnormal IHC (absent), MSI+

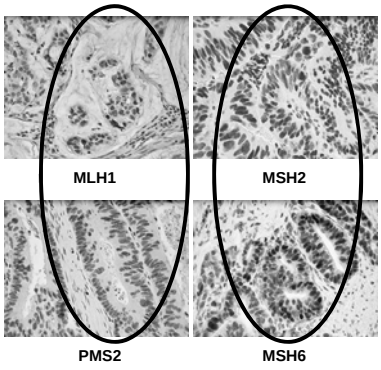


Identification of Lynch syndrome in the Genetics Clinic

- Can predict who is more likely to have LS using family history criteria (Amsterdam & Bethesda)
- Can predict the likelihood of a MMR gene mutation using on-line programs
  - PREMM1,2
  - http://www.dana-farber.org/pat/cancer/gastrointestinal/crc-calculator/
  - MMRpro http://www4.utsouthwestern.edu/breasthealth/cagene/
  - MMRpredict http://www1.hgu.mrc.ac.uk/Softdata/MMRpredict.php
- Can order MSI and/or IHC on tumor to screen for LS
- Can diagnose Lynch syndrome with genetic testing

Immunohistochemistry

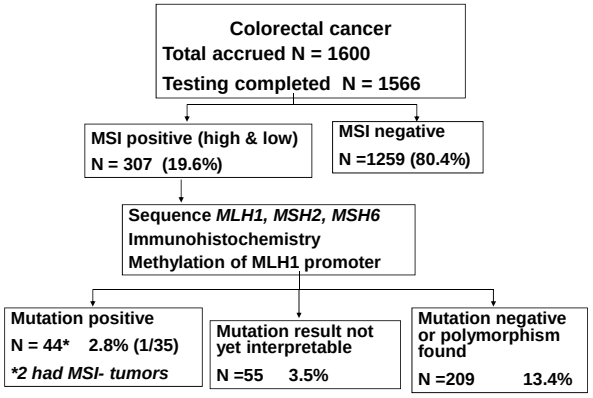
- Identify MMR proteins
- Normally present
- If protein is absent, gene is not being expressed (mutation or methylation)
- Helps direct gene testing by predicting likely involved gene
- If abnormal IHC (absent), MSI+



Identification of Lynch Syndrome among all Newly Diagnosed CRC Patients

- Unlikely to have good family history
- High volume
- Pathologists will know age at dx, synchronous primaries, but not likely to know all metachronous primary or family history of patients
- Must rely on screening tests for LS (MSI/IHC)

Columbus-Area Lynch syndrome Study



Hampel et al. NEJM 2005. & Hampel et al. JCO 2008.

Family Studies of 35/44 CRC Probands

35 CRC probands have had genetic counseling

Degree of Kinship	Tested	Positive
First	99	52
Second	64	28
> Second	86	29
Total	249	109

Hampel et al. NEJM 2005;352:1851-60.; Hampel et al. JCO 2008.

44 CRC Proband Characteristics

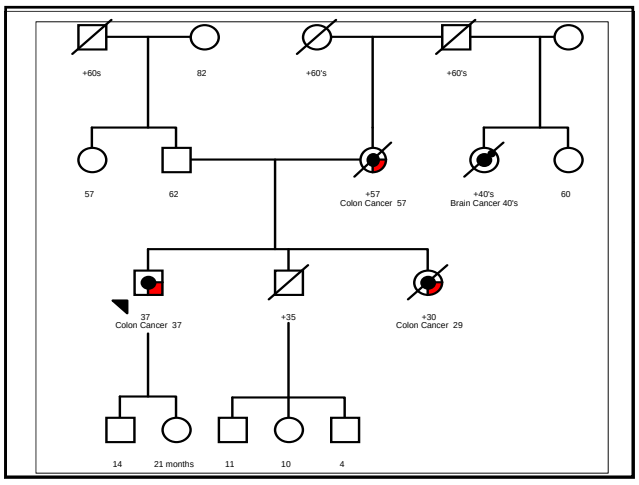
- Age at diagnosis – 51.4 (range 23-87)
- 50% diagnosed over age 50
- 25% did not meet either Amsterdam or Bethesda criteria
- Mutations
  - 20.5% *MLH1*
  - 52.3% *MSH2*
  - 13.6% *MSH6*
  - 13.6% *PMS2*

Hampel et al. NEJM 2005;352:1851-60.; Hampel et al. JCO 2008.

Familial Colorectal Cancer syndrome type X

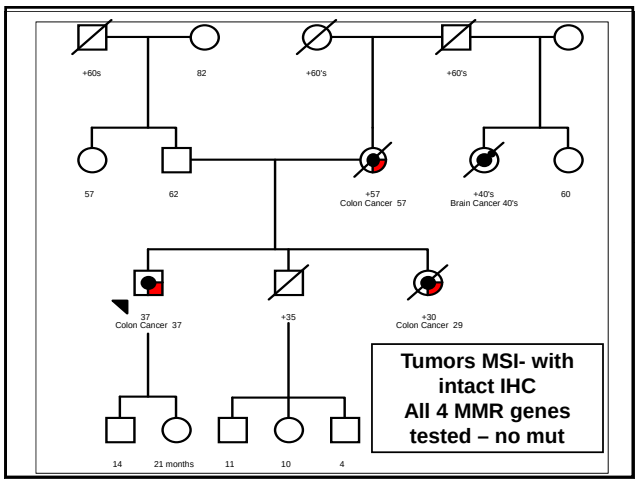
- ~40% of families that meet Amsterdam I criteria do not have an MMR gene mutation
- Only have increased risk for CRC
- CRC risk is lower than among families with MMR gene mutation (SIR 2.3 v 6.1)
- No testing available at this time
- Colonoscopy at least every 5 years beginning 5-10 years before the earliest CRC diagnosis in the family

Lindor et al. JAMA. 2005.



MUTYH-Associated Polyposis (MAP)

- Recessive – carrier frequency high (1/100)
- Biallelic mutations found in;
  - ≤ 1/3 of polyposis cases without APC mutations or evidence of vertical transmission
  - 0.2-6.7% of CRC dx <50 without polyps
- Y165C & G382D common in W.E. Caucasians
- E466X in Eastern Indian families



MAP Management

- Colonoscopy every 1-2 y begin at 25-30
- UGI endoscopy and side viewing duodenoscopy every 3-5 y begin at 30-35
- Subtotal colectomy or proctocolectomy depending on adenoma density and distribution

Familial Colorectal Cancer Risks

Table 1. Selected Familial Relative Risk (FRR) Estimates for Probands Considering Only First-Degree Relative (FDR) Family History

No. of affected FDRs	No. of probands	FRR (95% CI)
0	2,232,396	0.89 (0.87–0.91)
1	87,089	1.91 (1.82–2.00)
≥1	94,931	2.05 (1.96–2.14)
2	6966	3.01 (2.66–3.38)
3	762	4.43 (3.24–5.90)
4	92	7.74 (3.71–14.24)
≥5	22	19.86 (7.29–43.24)

Table 2. Familial Relative Risk (FRR) Estimates for Probands With 0 or 1 Affected First-Degree Relatives (FDRs) and Increasing Numbers of Affected Second-Degree Relatives (SDRs)

No. of affected FDRs	No. of affected SDRs	No. of probands	FRR (95% CI)
0	0	1,961,853	0.86 (0.84–0.88)
0	1	214,809	1.05 (0.99–1.11)
0	2	33,407	1.26 (1.09–1.38)
0	≥3	8527	1.48 (1.11–1.93)
1	0	65,192	1.82 (1.72–1.93)
1	1	16,760	2.12 (1.90–2.35)
1	2	5776	3.31 (2.83–3.84)
1	≥3	1365	3.37 (2.20–4.90)

Table 4. Selected Familial Relative Risks (FRRs) for Probands With Affected First-Degree Relatives (FDRs) or Second-Degree Relatives (SDRs) Diagnosed at Certain Ages

Proband	No. of probands	FRR (95% CI)
≥1 affected FDR diagnosed <50 y of age	4291	3.31 (2.79–3.89)
≥1 affected FDR diagnosed between 50 and 59 y of age	12,094	2.53 (2.24–2.85)
≥1 affected FDR diagnosed ≥50 y of age	89,340	2.02 (1.93–2.11)
≥1 affected FDR diagnosed between 60 and 69 y of age	26,084	2.22 (2.04–2.40)
≥1 affected FDR diagnosed ≥60 y of age	78,629	1.99 (1.90–2.09)
≥1 affected FDR diagnosed between 70 and 79 y of age	32,445	1.97 (1.83–2.12)
≥1 affected FDR diagnosed ≥70 y of age	56,065	1.97 (1.86–2.08)
≥1 affected SDR diagnosed <50 y of age	10,616	1.84 (1.61–2.09)

Taylor, DP, Gastroenterology 2010;138:877-886.

GINA

- **Prevents health insurers from denying coverage, adjusting premiums, or otherwise discriminating on the basis of genetic information.**
  - **Group and self-insured policies**
- **Insurers may not request that an individual undergo a genetic test.**
- **Employers cannot use genetic information to make hiring, firing, compensation, or promotion decisions.**
- **Sharply limits a health insurer's or employer's right to request, require, or purchase someone's genetic information.**

Familial Colorectal Cancer Screening Recommendations

- **FDR diagnosed <50**
  - **Colonoscopy every 3-5 years beginning at age 40**
- **FDR diagnosed 50-60**
  - **Colonoscopy every 5 years beginning at age 40**
- **FDR diagnosed >60**
  - **Colonoscopy every 5 years beginning at age 50**
- **Otherwise follow Average Risk recommendations**

Resources

- **Heather Hampel**
  - **614-293-7240**
  - **Heather.Hampel@osumc.edu**
- **Family Health*Link***
  - **https://familyhealthlink.osumc.edu**
  - **Free, on-line tool that assesses family history of cancer and cardiovascular disease**