Colorectal Cancer Screening

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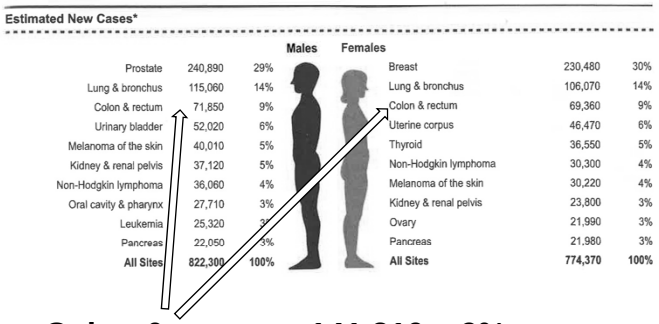
Colorectal Cancer Screening

Why?

Primary Goal is to Prevent Deaths from Colon Cancer

Estimated new cancer cases U.S. 2011

Estimated New Cases

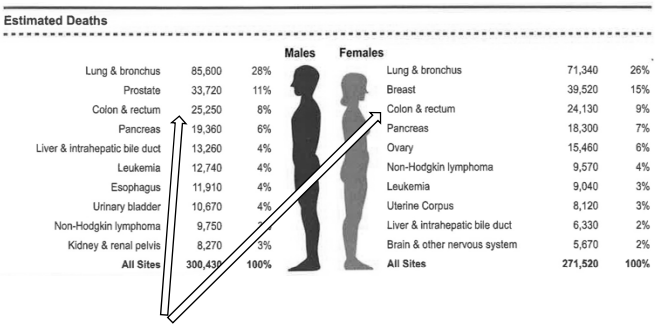


Colon & rectum 141,210 9%

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

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: Early detection

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

Colorectal Cancer Survival Rates

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

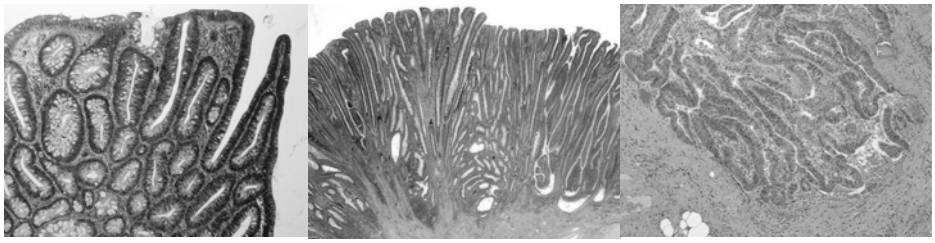
Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localized (confined to primary site)	39	90.1
Regional (spread to regional lymphnodes)	37	69.2
Distant (cancer has metastasized)	20	11.7
Unknown (unstaged)	5	33.3

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

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***

The Downside of CRC Screening Effectiveness

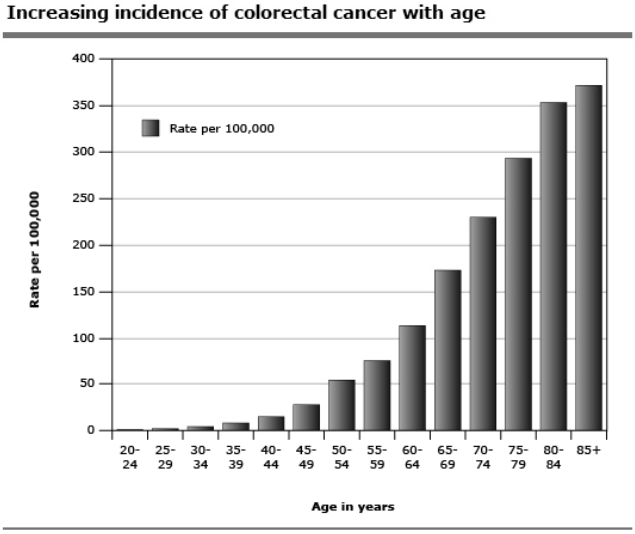
- **Only about half of people 50 years or older undergo screening**
- **Only 4/10 cancers are detected at an early stage**
- **Lack of public or professional awareness**
- **Financial barriers**

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**

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**

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.

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

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

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**

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**

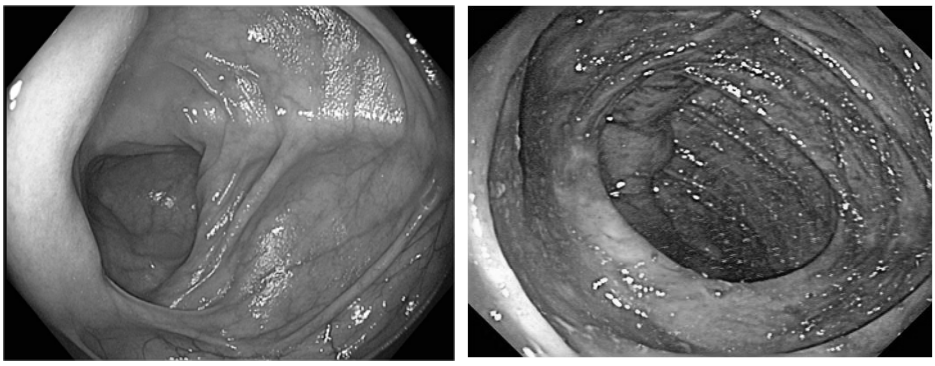
Consensus Guideline 2008: ACS, US Multi-society Task Force on Colorectal Cancer, American College of Radiology

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)**



Images provided courtesy of Dr. Douglas Rex of IUPUI.

2009 Colon Cancer Screening Guidelines from the American College of Gastroenterology

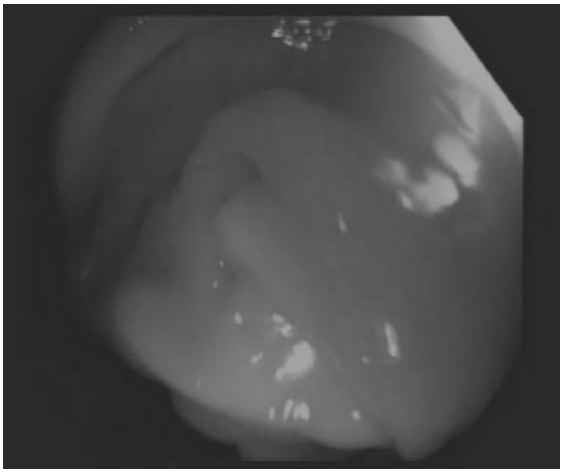
- CT colonography performed every 5 years is an alternative for patients who decline colonoscopy
- Barium enema is not recommended for CRC screening/prevention
- Fecal testing is a cancer DETECTION test, not a PREVENTION test; fecal immunohistochemical testing (FIT) replaces the older guaiac-based fecal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

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]**

Good Withdrawal technique



Video provided courtesy of Dr. Douglas Rex of IUPUI.

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

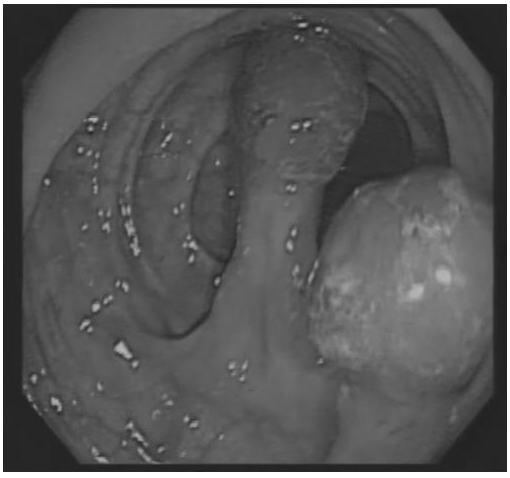
Specific Screening Tests

- 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

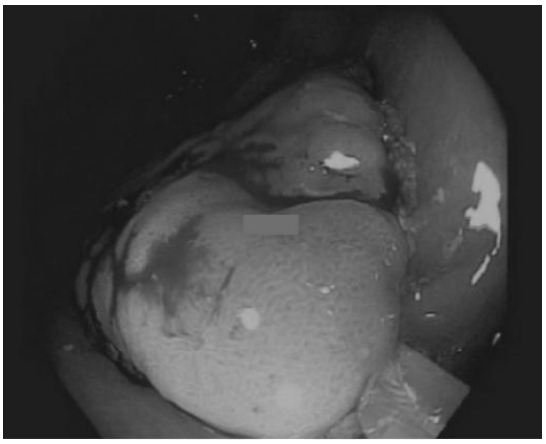
- **CT Colonography**
  - **Multiple CT images**
  - **Bowel prep required to reduce false positives created by residual stool**
  - **Colonoscopy recommended for polyps >6 mm**
  - **Air insufflation required**
  - **Diagnostic yield for cancers and polyps over 10 mm is similar to colonoscopy**
  -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

Final Peduncalated video



Video provided courtesy of Dr. Douglas Rex of IUPUI.

Central Injection 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

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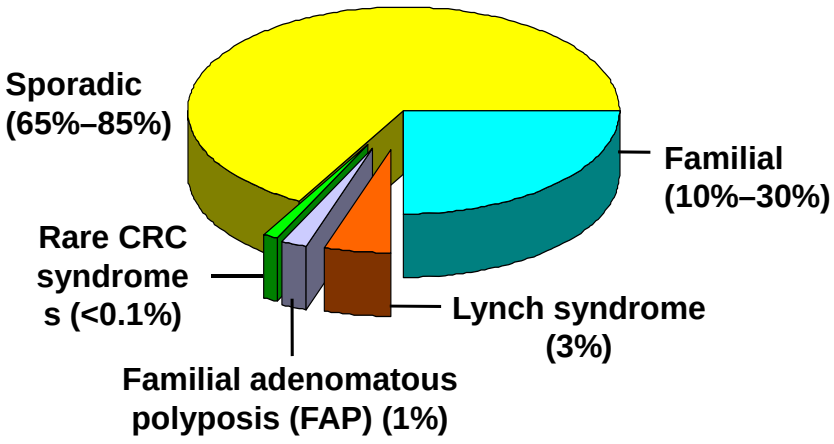
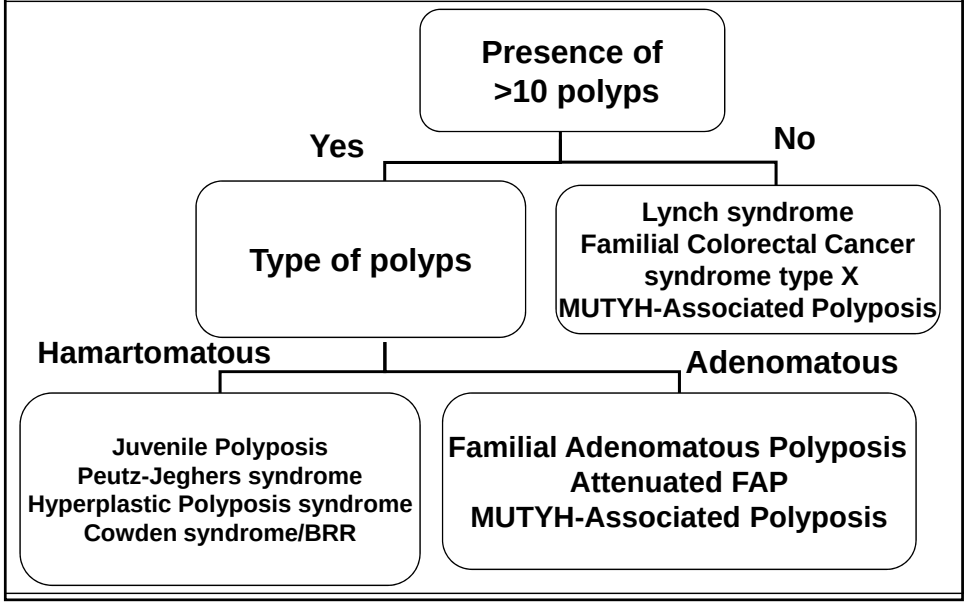
Hereditary susceptibility to CRC

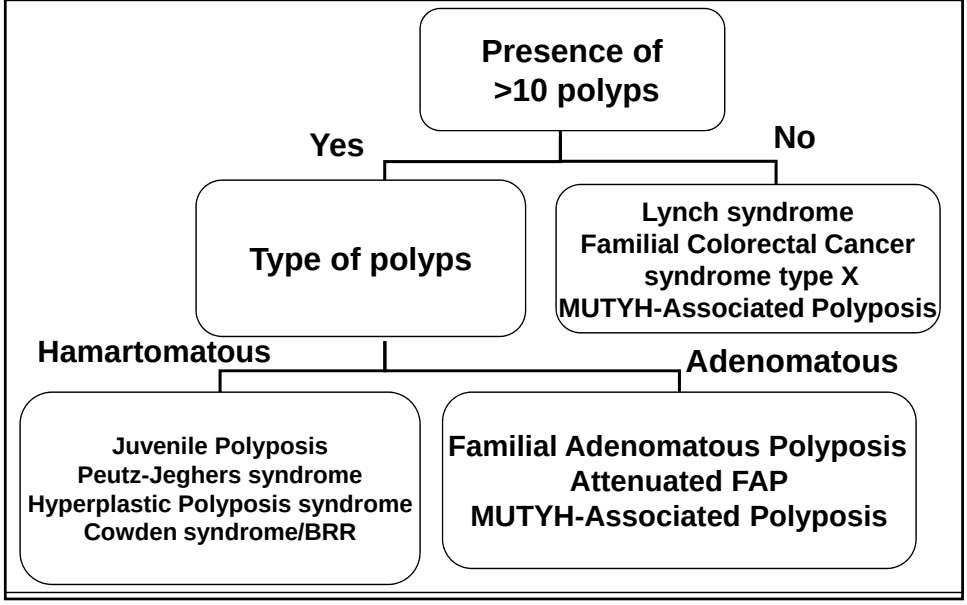


Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996

Flowchart for Hereditary Colon Cancer differential diagnosis

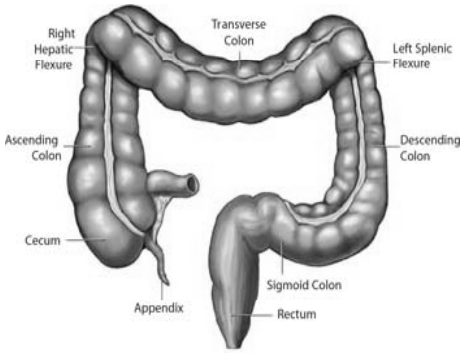


Flowchart for Hereditary Colon Cancer differential diagnosis



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 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 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

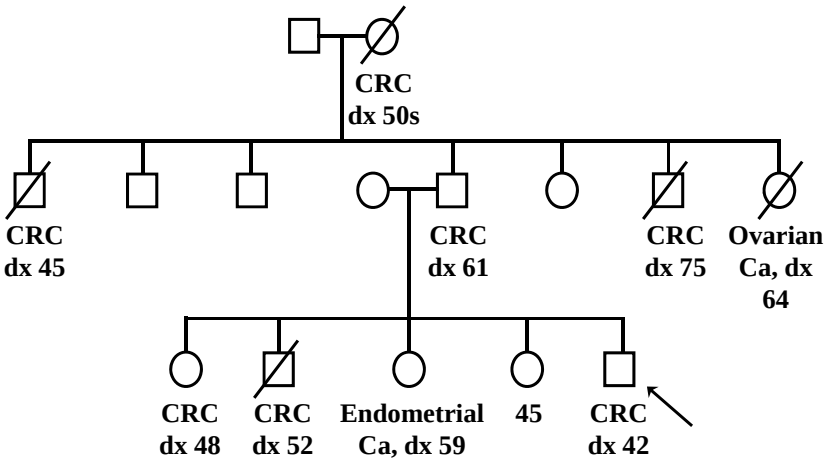
Lindor N et al. JAMA 2006;296:1507-17. & Vasen HFA et al. J Med Genet 2007;44:353-62.

Lynch Syndrome 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?



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

Bethesda Guidelines

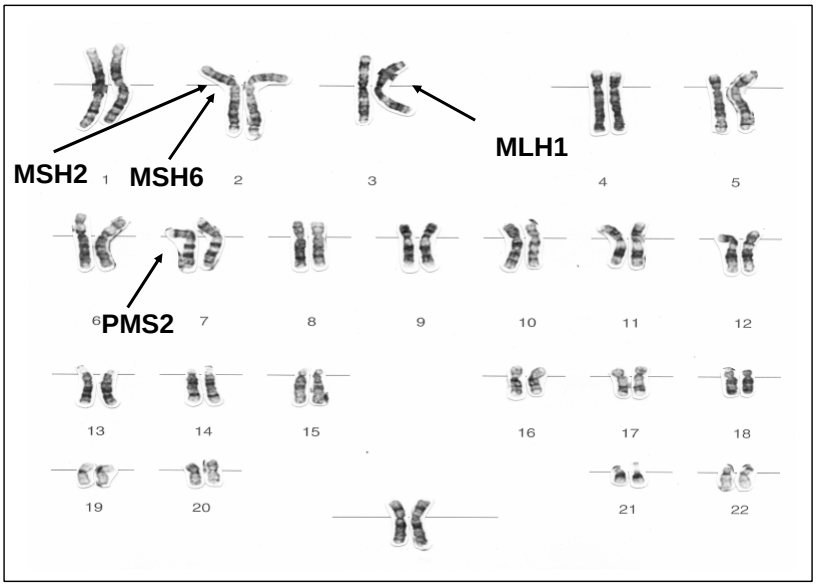
- CRC dx <50
- Synchronous or metachronous CRC, or other HNPCC-associated tumors regardless of age
- CRC with MSI-H histology dx <60
- CRC with ≥1 FDR with an HNPCC-associated tumor, with one cancer dx <50
- CRC with ≥2 FDRs or SDRs with an HNPCC-associated tumor, regardless of age

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

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

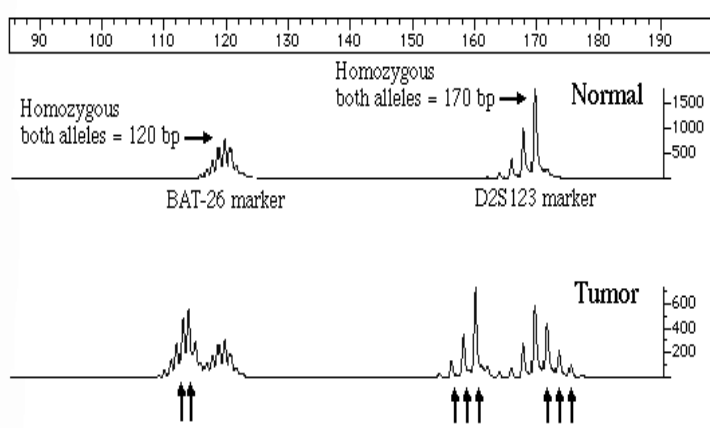
Lynch Syndrome Genes



Microsatellite Instability (MSI)

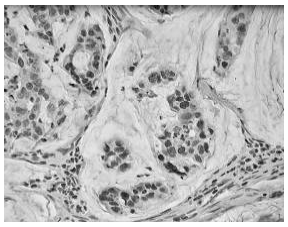
- Repetitive DNA sequences 1- 4 nucleotides (microsatellites) normally found genome
  - Mono: TCGAGG AAAAAAAA GGAGCT
  - Di: TCGAGG CACACACACACA GGAG
- With MMR failure, variability in repeats
- 95% of HNPCC tumors are MSI+
- 10%–15% of sporadic CRCs are MSI+

MSI testing on Genotyper

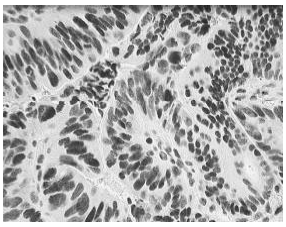


Immunohistochemistry

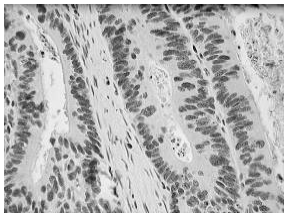
- **Identify MMR proteins**
- **Normally present**
- **If protein is absent, gene is not being expressed (mutation or methylation)**
- **Helps direct gene testing by predicting likely involved gene**
- **If abnormal IHC (absent), MSI+**



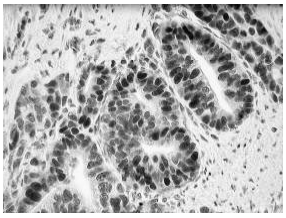
MLH1



MSH2



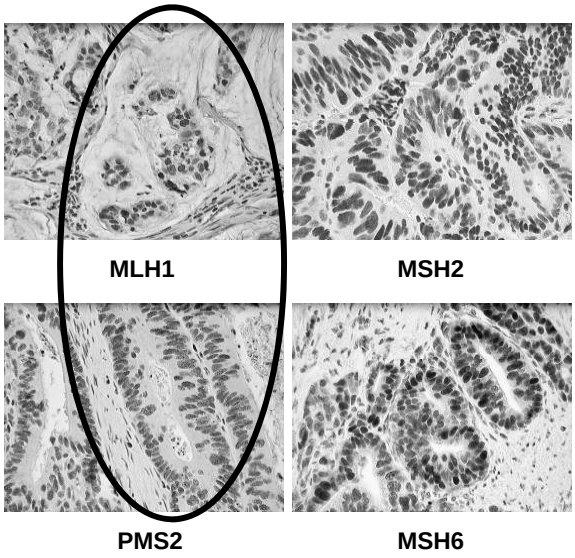
PMS2



MSH6

Immunohistochemistry

- Identify MMR proteins
- Normally present
- 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+



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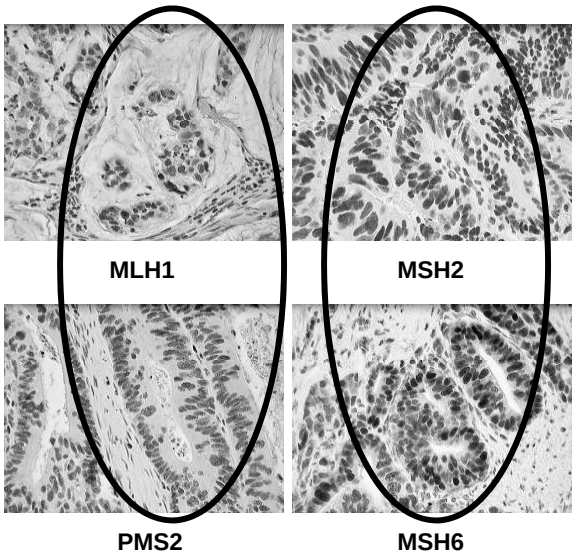


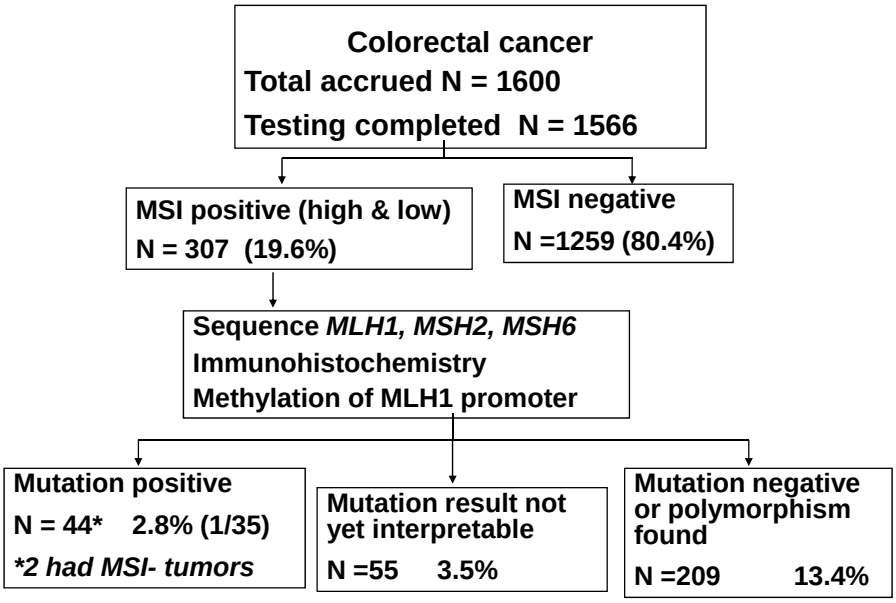
Identification of Lynch syndrome in the Genetics Clinic

- 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

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.

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.

Family Studies of 35/44 CRC Probands

35 CRC probands have had genetic counseling

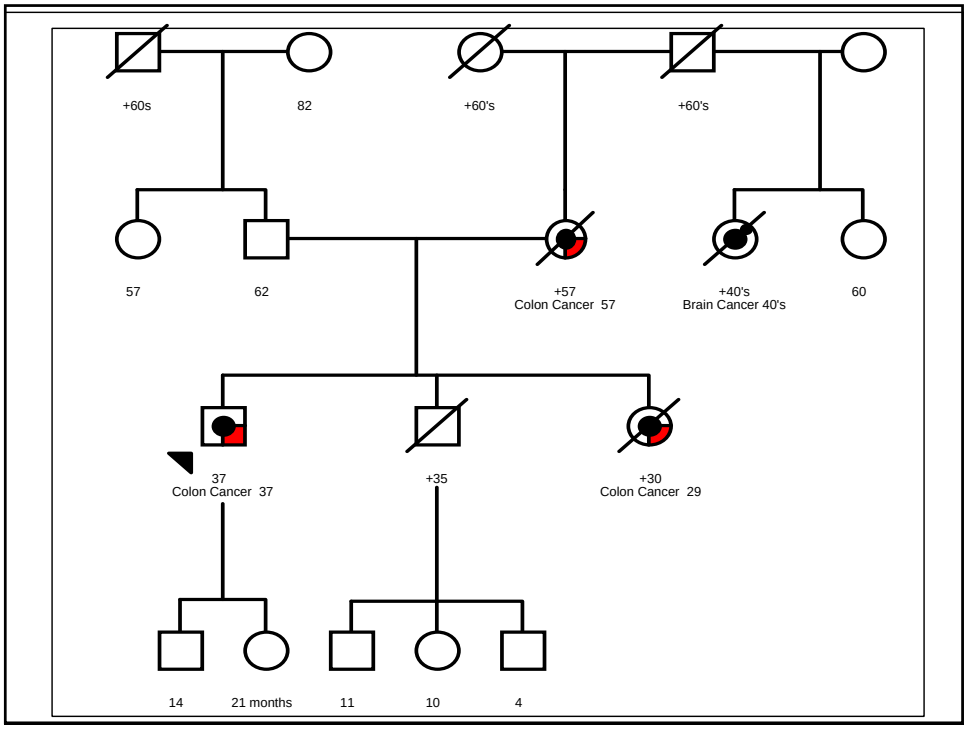
Degree of Kinship	Tested	Positive
First	99	52
Second	64	28
> Second	86	29
Total	249	109

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

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.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Colon Cancer 57
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Brain Cancer 40's
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Colon Cancer 37
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Colon Cancer 29
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21 months
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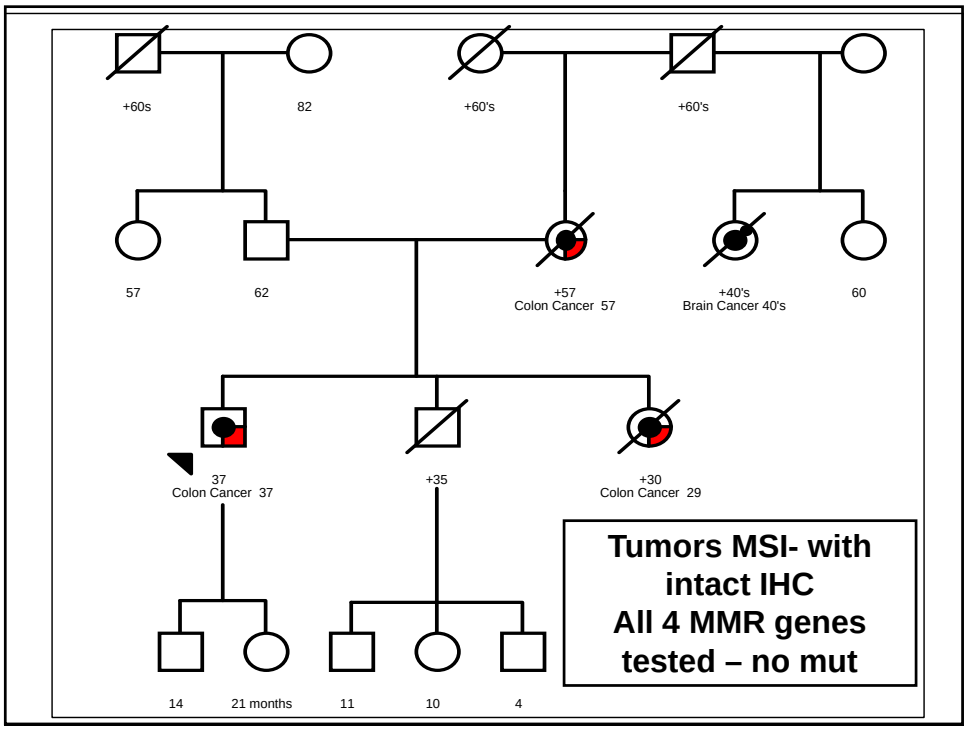
+60s
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Colon Cancer 37
+35
+30
Colon Cancer 29
14
21 months
11
10
4
Tumors MSI- with intact IHC
All 4 MMR genes tested – no mut

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	1,965,853	0.86 (0.84–0.88)
0	1	224,609	1.05 (0.99–1.11)
0	2	33,407	1.20 (1.05–1.38)
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	3776	2.31 (1.80–2.93)
1	≥3	1361	3.37 (2.20–4.93)

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	6291	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	25,084	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	19,616	1.84 (1.61–2.09)

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

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**

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.**

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**