Colorectal Cancer (CRC) Screening & Inherited Risk Gastrointestinal Cancer

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CRC in USA

- Lifetime-Risk of CRC is 4.7% (1/20)
  - 132700 cases of CRC in 2015
    - 93090 cases of colon Ca, and 39610 of rectal Ca in 2015.
  - More than 9 in 10 are older than age 50.
    - Between ages 50-70, 2.04% males & 1.53% women will develop CRC

CRC in USA

- Mortality:
  - 56000 per year;
    - decreasing 2.5% per year in part due to early detection;
    - more than half could have survived if they had CRC screening.
  - 10% of cancer deaths
  - 2.3% of all deaths
  - Second cancer killer after Lung Cancer (men + women combined)
  - Third cause of cancer death in both, men and women.
  - First cause of Cancer death in non-smokers

CRC: Among "Most-Preventable" but "Least Prevented" of Cancers

- Almost always curable if detected early.
- Average "lead-time" from colon adenoma to "advanced cancer" is 10 years.
- 25% of people older than 50 have colon polyps (adenomas found in 30% of men & 20% of women)
- 20% of colon adenomas become cancerous
- Colonoscopy + polypectomy decreases CRC by up to 90%.

CRC: Among “Most-Preventable” but “Least Prevented” of Cancers

- Half of colon Cancer patients die from CRC.
- Screening is underused: 1 in 3 of persons age 50-75 are not getting screened.
- Medicare can save15 billion dollars if we screen for CRC with colonoscopy all persons age 50-64.
- Cost Effective: Cost per year of life saved is $15,000 to 50,000 USD, until age 83
- Usually Screening is discontinued at age 75 in “average risk”, or when life expectancy < 10 years.

Screening

Screening refers to examinations that are performed in an asymptomatic population in an attempt to identify preclinical disease and alter its natural history so as to reduce morbidity and mortality.

Risk if Interval Cancer after negative screening colonoscopy or polypectomy is 1.1-2.7 per 1000 person-years or 0.23 to 0.69 of expected (mostly because up to 17% of lesions > 10 mm are missed with colonoscopy).

CRC Screening Recommendation

- **Everybody should be risk-stratified for CRC around age 20 & again at age 30, 40 and 50.**
  - Personal History of colon Adenoma or CRC
  - Illness that predisposes to CRC: IBD, Cystic Fibrosis, Abdominal radiation for childhood cancer
  - Family History of colon Adenoma, hereditary syndrome associated with increased risk, serrated polyposis syndrome or CRC
    - **degree of relation**
      - **1st = parent/sibling/child, vs**
      - **2nd = grandparent/aunt/uncle, vs**
      - **3rd = great-grandparent/cousin.**
    - **how many relatives affected,**
    - **earliest age of presentation.**

CRC Screening Recommendation

- **Average-risk for CRC**
  - Asymptomatic, and
  - Answered NO to all “risk-questions” for CRC or colon adenoma.
  - Should be offered screening for CRC beginning at age 50
    - age 45 for African Americans as per Multi-society Task Force in CRC.

CRC Screening Recommendation

- **Increased-risk & High-risk for CRC**
  - Asymptomatic, and
  - Answered YES to one or more “risk-questions” for CRC or colon adenoma.
  - **Should be offered screening with an onset and frequency commensurate to the degree of risk.**

Successful CRC Screening

- Physician must offer it
- Patient must accept advice
- Insurers must pay screening
- Patient-care organizations must track whether screening was done and give reminders.
- Work-force should be in place
- Patient must take bowel preparation (split-day)
- Provider should perform test correctly
- Patient and PCP must remember when next screening test is due.

Barriers to Screening for CRC

NYC Community Health Survey 2006

- Lack of insurance (30% gap)
- Lack of Primary Care Physician (25% gap)
- Extreme poverty (15% gap)
- Smoking (13% gap)
- Non-Caucasian (10% gap)
- Foreign born (10% gap)
- Low education level (8% gap)

Relative Risk by Lesion Type

Classification of Colon Polyps

Adenomas and Serrated Lesions

- I. Conventional adenomas
  - a. Dysplasia grade
    - i. High grade
    - ii. Low grade
  - b. Villousity
    - i. Tubular
    - ii. Tubulovillous
    - iii. Villous
- II. Serrated lesions
  - a.Hyperplastic polyps (not considered precancerous)
  - b. Sessile serrated polyp
    - i. Without cytologic dysplasia
    - ii. With cytologic dysplasia
  - c. Traditional serrated adenoma

IMPORTANT CONCEPT

Low Risk Lesions

- 1 – 2 Tubular Adenomas with no dysplasia or low grade dysplasia and < 10 mm.
- Sessile Serrated Polyp < 10 mm and without Dysplasia.
- **Surveillance intervals of 5 to 10 years are adequate. The 5 year interval is preferred i colon prep was suboptimal or cecal intubation was not done.**

IMPORTANT CONCEPT
High Risk Lesions

- High Risk Adenomas:
  - Adenoma Sized 1.0 cm or larger OR
  - Adenoma with any villous component (nontubular) OR
    - Tubulo-villous (25-75% villous); villous (> 75% villous)
  - Adenoma with "High-Grade" Dysplasia (HGD) OR
  - Adenoma with "Invasive" cancer
- 3 or more adenomas (any size or histology), OR
- Traditional Serrated Adenoma, OR
- Sessile Serrated Polyp (SSP) >/= 10 mm, OR
- Sessile Serrated Polyp (SSP) with Dysplasia.
- **High Risk Lesions are a surrogate biological-indicator of cancer risk. Need short Surveillance Interval.**

IMPORTANT CONCEPT
Serrated Adenoma

- Hyperplastic polyp with mixed features of Hyperplastic and Adenomatous polyp.
  - Sessile Serrated Adenoma or Polyp (SSA) (usually without dysplasia; if dysplastic will be called “Mixed Serrated Polyp”); 80% are proximal.
  - Traditional Serrated Adenoma (TSA) (villiform projections with dysplastic cells); they are mostly in distal colon (sigmoid/rectum).
  - Serrated polyps proximal to sigmoid colon are higher risk than distal ones.
- 20-30% of “Sporadic CRC” comes from Serrated Adenomas or Polyps.
- Serrated Adenomas are usually proximal, large, pale, sessile, often covered with mucus.

IMPORTANT CONCEPT
Serrated Adenoma

- Linked to ‘sporadic microsatellite instability adenocarcinoma’ – due to acquired mismatch repair deficiency (BRAF or CpG Island Methylator Phenotype (CIMP))
- The risk of malignant transformation is higher with SSA than with the others, but all have increased risk.
- Criteria of “Advanced Adenoma” also applies to Serrated Adenomas.
- **For Surveillance Programs, “Serrated Adenomas” should be treated as regular adenomas.**

IMPORTANT CONCEPT

Hyperplastic Polyps (HP)

- HP < 10 mm are benign and non neoplastic.
- HP are 50% of polyps 1-5 mm, 27.9% of polyps 6-9 mm, and 13.7% of polyps > 10 mm.
- Neither proximal nor distal HP associated with adenomas are indicative of increased risk of adenomas at 3 y after colonoscopy.
- If the only lesions at colonoscopy are distal HP < 10 mm, the next colonoscopy should be in 10 years.
- Proximal HP > 10 mm should raise the concern of being misclassified “Serrated Polyps”.

Screening Tools for CRC

Estimated sensitivity, specificity, and cancer-specific deaths averted for each colorectal cancer screening strategy

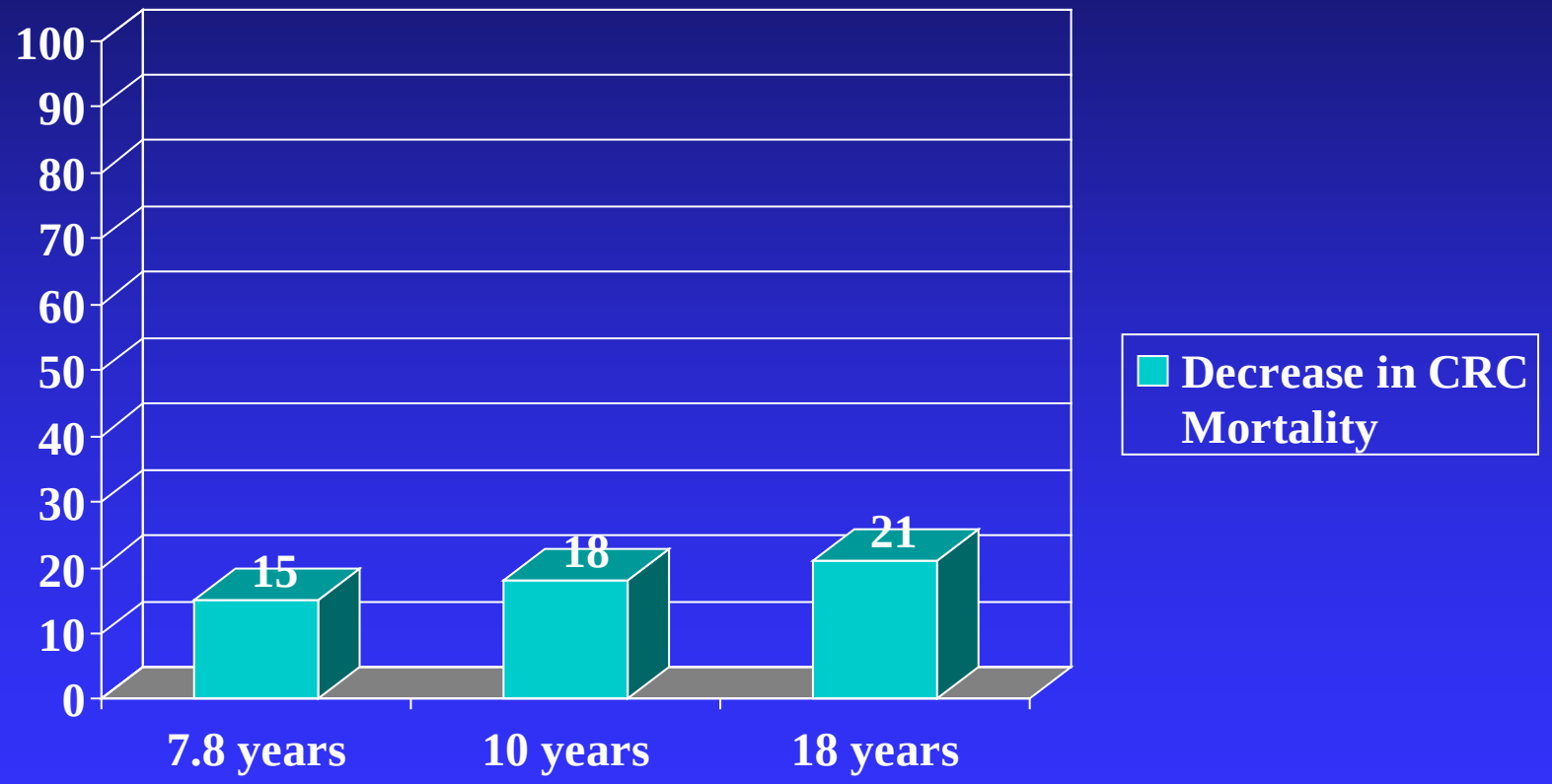
	Colonoscopy	Fecal immunochemical test (FIT)	Highly sensitive guaiac-based gFOBT	FIT-DNA Cologuard	Sigmoidoscopy*	Computed tomography colonography
Sensitivity (%)						
Adenomas 1 to 5 mm	75	7.6	7.5	17.2	75	–
Adenomas 6 to 9 mm	85	7.6	12.4	17.2	85	57
Adenomas ≥10 mm	95	23.8	23.9	42.4	95	84
Colorectal cancer	95	73.8	70	92.3	95	84
Specificity (%)	86	96.4	92.5	89.8	87	88
Colorectal cancer deaths averted per 1000 40-year-olds¶	22 to 24	20 to 23	20 to 23	21 to 24	16 to 21	16 to 24

Testing Alternatives

CA Cancer J Clin 2008

- **Highly Sensitive FOBT every year**:
  - Rationale:
    - Advanced colon adenomas and adenocarcinomas bleed intermittently.
  - Guaiac-test (Hemoccult Sensa) with diet restrictions, **or** immunochemical-test (Hemoccult ICT or HemeSelect) without diet restrictions;
  - 2-samples from each of 3 consecutive soft/formed stools,
  - without rehydration,
  - If FIT is (+): 14.3% will have “advanced adenoma”, and 6.2% colo-rectal CA.
  - **Positive-test followed by colonoscopy.**

Effect of Biennial Guaiac Testing Without Rehydration on CRC Mortality



Testing Alternatives

CA Cancer J Clin 2008

- **Flexible sigmoidoscopy (FS) every 5 years**
  - Rationale:
    - Decreases CRC in recto-sigmoid by 2/3
    - Only 2-5% of patients without distal adenomas have proximal “advanced adenomas”.
    - FS followed by colonoscopy if a polyp is found, will identify 70-80% of patients with advanced proximal neoplasia and decreases CRC incidence by 80%

Testing Alternatives

CA Cancer J Clin 2008

- **Combined yearly Highly Sensitive FOBT & Flexible Sigmoidoscopy every 5 years.**
  - Rationale:
    - Highly Sensitive FOBT helps to detect non-screened proximal colon lesions; increases "advanced neoplasia" detection.
  - Should be done:
    - first yearly Highly Sensitive FOBT x 4 y, then
    - FS every 5th year.
  - No prospective studies have evaluated this approach.

Fecal immunochemical testing (FIT)

- Measures hemoglobin in stool
- Single stool sample without diet nor medication restriction; better if quantitative.
- If Testing delayed > 5 days, sensitivity decreases. Best if tested within 24 h.
- May have degradation by high temperature.
- Repeated Yearly.
- Less sensitive for Right side lesions.
- In average CRC risk: CRC detection Sensitivity 74-80%; specificity 94%; For adenomas > 1 cm: 24%

Testing Alternatives

CA Cancer J Clin 2008

- **CT Colonography every 5 years**
  - Rationale:
    - using integrated 2D & 3D, >/= 16 slice scan technique + bowel prep + good distention +/- “stool tagging”.
    - In 1233 asymptomatic patients showed 94% sensitivity for large (>/= 10 mm) adenomas; per patient sensitivity for adenomas >/= 6 mm was 89%.
    - In meta-analyses, Sensitivity/Specificity for:
      - 1) adenoma >/= 10 mm = 88%/97%,
      - 2) Polyps 6-9 mm = 78%/89%,
      - 3) Invasive CRC = 96%

Capsule Colonoscopy

- Approved for previous incomplete colonoscopies and for patients who need colorectal imaging but who are not candidates for colonoscopy.
- Screening trial in 884 patients, capsule colonoscopy had:
  - 88% sensitivity for conventional adenoma ≥6 mm,
  - ineffective for the detection of serrated lesions,
  - 9% of patients had technically failed examinations for inadequate cleansing or rapid transit of the capsule

Cologuard (FIT + DNA Testing)

- Detects 92 % of colorectal cancers and 42 % of advanced adenomas in the study population (FIT screening test detects 74 % of cancers and 24 % of advanced adenomas).
- Cologuard ($ 600) stoolDNA component is less accurate than FIT at correctly identifying subjects negative for colorectal cancer or advanced adenomas. Cologuard correctly gave a negative screening result for 87 % of the study subjects, while FIT provided accurate negative screening results for 95 % of the study population.
- Repeated every 3 years in ONLY in AVERAGE RISK CRC
- Covered for Medicare beneficiaries age 50-85 every 3 years, only if
  - Asymptomatic, and
  - Average CRC Risk.

Testing Alternatives

CA Cancer J Clin 2008

- **Colonoscopy every 10 years**
  - Greater cost, risk, and inconvenience.
  - Rationale:
    - Half of patients with “advanced proximal adenoma” have no distal colonic neoplasia (will be missed by FS).
    - 65% of patients with colon Ca proximal to the splenic flexure had no distal neoplasia (will be missed by FS)
    - 22-30% of adenomas are “flat” or “depressed” (not visible by X-ray studies)

Testing Alternatives

CA Cancer J Clin 2008

- **Colonoscopy every 10 years**
  - Only 6% or less of “advanced adenomas” are missed by colonoscopy.
    - Decreases incidence and mortality of distal CRC by 80%, and of proximal CRC by 40-60% in USA.
  - Colonoscopy decreases CRC incidence in patients with adenomas
  - Dwell time from colorectal adenoma to carcinoma is on average at least 10 years; allows long intervals between exams.
  - In 154 average-risk persons with initial negative colonoscopy, < 1% had advanced adenoma 5 years later.
  - Risks of perforation, bleeding, and death of 0.5 per 1000, 2.6 per 1000, and 2.9 per 100,000

IMPORTANT CONCEPT
High-quality Baseline Colonoscopy

- HQC should be satisfied before starting colonoscopy-based Screening or Surveillance Program.
- Is critical for effectively reducing colon cancer risk.
- Requirements of “High-quality” Colonoscopy:
  - Reaches cecum (photodocumentation)
  - Little fecal residue (good prep)
  - Minimum time of withdrawal from the cecum of 6-10 minutes
  - Meticulous removal of large sessile polyps – particularly if piecemeal polypectomy was used (repeat exam if needed)

CRC SCREENING TIER CHOICE US Multi Society Task Force 2017

Tier 1
Colonoscopy every 10 years
Annual fecal immunochemical test
Tier 2
CT colonography every 5 years
FIT-fecal DNA every 3 years
Flexible sigmoidoscopy every 10 years (or every 5 years)
Tier 3
Capsule colonoscopy every 5 years
Available tests not currently recommended
Septin 9

Stratification of CRC Screening by Risk Factors

Average Risk for CRC

- "High Quality" Colonoscopy every 10 years
- No FOBT testing in the interval.
- Colonoscopy repeated early only if symptoms develop.
- If adenoma or adenocarcinoma is found, patient should be placed in CRC Surveillance Program.

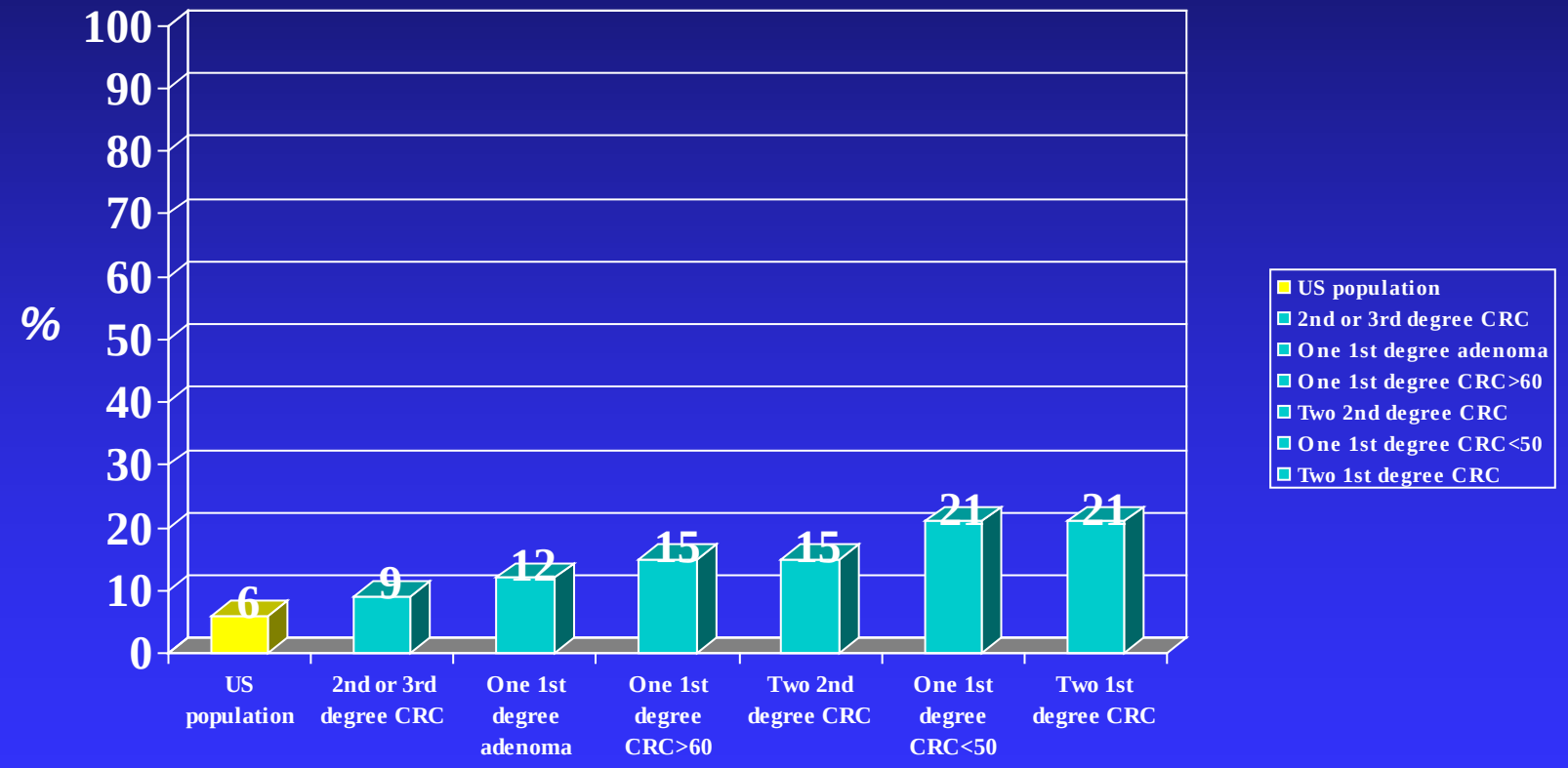
When to Stop Screening for CRC

- At age 75 if all previous screening test were negative.
- At age 75 if life expectancy is < 10 years.
- Up to age 85 if NO PREVIOUS SCREENING has been done, depending in co-morbidities.

Increased-Risk for CRC

Familial Risk

Familial Risk
Lifetime Risk of CRC



Effect of Family History on Onset & Frequency of Screening Colonoscopy (2017)

Category	Start age (the lesser)	Interval
One 2nd degree or more, or any number 3rd degree with CRC: Assess if HNPCC; if not	50 (45 in African Americans)	10 years
One 1st degree with CRC, or PROVEN Advanced Adenoma, or Advanced Serrated lesion =/> age 60	40	10 years
=/> Two 1st degree with CRC or PROVEN Advanced Adenoma, or Advanced Serrated lesion, at ANY AGE	40, or [10 y before "index"]	5 years
One 1st degree with CRC, or PROVEN Advanced Adenoma, or Advanced Serrated lesion < age 60	40, or [10 y before "index"]	5 years
Family Colon Cancer Syndrome X (HNPCC criteria (+) without Hereditary DNA mismatch Repair gene mutation)	10 years before youngest affected relative	3-5 years
HNPCC	See specific Guideline	

High-Risk for CRC

-Inflammatory Bowel Disease

-Inherited Colorectal Cancer Disorders

-Abdominal radiation in childhood for malignancy (start at age 30)

-Cystic Fibrosis: start at age 40, or 2 year after organ transplant (if older than 30)

Inflammatory Bowel Disease
CRC Risk in UC

- CRC risk in UC is estimated at:
  - 2% after 10 years,
  - 8% after 20 years, and
  - 18% after 30 years of disease.
- UK 30-year surveillance program, CRC and dysplasia risk:
  - 7.7% at 20 years and
  - 15.8% at 30 years.
- In population-based studies CRC risk may not be this high and the risk has decreased over time. This may be due to:
  - use of aminosalicylates (chemoprotective effect),
  - liberal and early use of colectomy for medically refractory disease,
  - surveillance colonoscopy.

Inflammatory Bowel Disease
CRC Risk in CD Colitis

- Two meta-analyses have reported the:
  - standardized incidence ratio for CRC as 2.5 (95% confidence interval [CI], 1.7–3.5) and
  - relative risk (RR) as 4.5 (95% CI, 1.3–14.9).
- Studies of patients with UC or CD colitis have shown the risk to be roughly equivalent in both diseases (RR of 2.75 and 2.64, respectively).
- Many of the characteristics of CRC in UC and CD have been shown to be similar.
- Thus, extensive Crohn's colitis (> 1/3 of colon) should raise the same concerns regarding CRC risk as UC.

Factors Other Than Dysplasia That Increase or Decrease the Risk of CRC in IBD

- Increased Risk:
  - disease duration,
  - more extensive disease (above sigmoides),
  - primary sclerosing cholangitis (4X), and
  - family hx of sporadic CRC (1^{st} degree relative: 2X if > 50, 9X if < 50)
  - colonic strictures in patients with UC
  - a shortened colon in UC,
  - multiple postinflammatory pseudopolyps in UC
  - Inflammation (histological, not only macroscopic)
- No increased risk:
  - Proctitis, or
  - Proctosigmoiditis (defined as any histological dz)

Inflammatory Bowel Disease

- No good RCTs; based on expert opinion
- Recommendation apply to all Ulcerative Colitis and Crohn's Disease colitis involving at least 1/3 of the colon.
- Start screening after:
  - 8 years of "Pan-Colitis" or
  - 15 years of "Left-sided Colitis"
- If coexisting diagnoses of UC/CD colitis and PSC – start surveillance immediately.
- Surveillance colonoscopy every 1-2 yrs with either:
  - biopsies in 4 quadrants at every 10 cm from cecum to mid-sigmoid, then every 5 cm in the distal 25 cm, **(>/= 33 Bx)** or
  - with 0.2% indigocarmine chromoendoscopy-guided "smart biopsies" **(Itzkowitz SH et al. Inflamm Bowel Dis 2005; 11:314-321)**

Gastroenterology 2010;138:738-745 and
American Journal of Gastroenterology - 2004 – Ulcerative Colitis Practice Guidelines

CRC Screening & Surveillace in Inflammatory Bowel Disease

- All patients, regardless of the extent of disease at initial diagnosis, should undergo a screening colonoscopy a maximum of 8 years after onset of symptoms.
- Patients with ulcerative proctitis or ulcerative proctosigmoiditis are not considered at increased risk for IBD-related CRC and may be managed as average-risk.
- Patients with extensive or left-sided colitis should begin surveillance within 1 to 2 years after the initial screening endoscopy.
- The optimal surveillance interval has not been clearly defined. After 2 negative examinations (no dysplasia or cancer), further surveillance examinations should be performed every 1 to 3 years.
- A minimum of 33 biopsy specimens be taken in patients with pancolitis.

CRC Screening & Surveillance in Inflammatory Bowel Disease

- Chromoendoscopy with targeted biopsies is recommended as an alternative to random biopsies
- Patients with PSC should begin surveillance colonoscopy at the time of this diagnosis and then undergo yearly colonoscopy thereafter
- Ideally, surveillance colonoscopy should be performed when the colonic disease is in remission.
- Patients with a history of CRC in first-degree relatives, ongoing active endoscopic or histologic inflammation, or anatomic abnormalities such as a foreshortened colon, stricture, or multiple inflammatory pseudopolyps may benefit from more frequent surveillance examinations (probably yearly).
- These recommendations also apply to patients with Crohn's colitis who have disease involving at least one third of the length of the colon.

Management of Flat Dysplasia in IBD

- Grade A: There is high certainty that colectomy for flat HGD treats undiagnosed synchronous cancer and prevents metachronous cancer.
- Grade Insufficient: The current evidence is insufficient to assess the balance of benefits and harms of colectomy for flat LGD.
  - If flat LGD detected in biopsy specimens is:
    - found at the time of initial screening (prevalent dysplasia), or
    - found on more than one occasion, or
    - multifocal (detected at more than one site in the colon).
  - stronger consideration should be given to recommending colectomy

Management of Raised Dysplasia in IBD

- I. Patients with IBD and a non–adenoma-like dysplasia associated lesion or mass (DALM) should be treated with colectomy. Non-adenoma-like DALM include:
  - velvety patches,
  - plaques,
  - irregular bumps and nodules,
  - wart-like thickenings,
  - stricturing lesions, and
  - broad-based masses

Management of Raised Dysplasia in IBD

- II. Patients with IBD and an adenoma-like dysplasia-associated lesion or mass (DALM), and no evidence of flat dysplasia around the polyp or elsewhere in the colon, can be managed safely by polypectomy and continued surveillance. Adenoma-like DALM are:
  - well-circumscribed, smooth or papillary, non-necrotic, sessile or pedunculated polyps that are usually readily accessible to removal.

Effect of IBD on Onset & Frequency of Screening Colonoscopy

Category	Start time	Interval
Pancolitis	> 8 years of disease	2 years; q 1 y after 20 y of IBD
Left sided colitis	> 15 years of disease	2 years; q 1 y after 20 y of IBD
Colitis associated with Primary Sclerosing Cholangitis	At time of diagnosis	1 year
IBD colitis with 1st degree relative with CRC (consider also for: histologic inflammation, foreshortened colon, stricture, or multiple inflammatory pseudopolyps)	Pancolitis x 8 y Left sided colitis x 15 y	1 year

Inherited CRC Disorders

Hereditary CRC Syndromes

Syndrome	Gene(s)	Features
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	CRC, endometrial/ovarian, urothelial, brain, small bowel, skin (sebaceous adenoma/carcinoma)
Familial Adenomatous Polyposis	APC	Adenomas, CRC, duodenal, gastric and thyroid cancer, osteomas, soft tissue tumors, desmoid tumors
MYH-Associated Polyposis*	MUTYH	Adenomas, colon cancer, thyroid cancer
NTHL1- associated polyposis*	NTHL1*	Adenomas (oligopolyposis), endometrial, CRC
Polymerase proofreading associated polyposis	POLE, POLD1	Adenomas (oligopolyposis), endometrial, brain cancer
Peutz-Jeghers Syndrome	STK11	Mucocutaneous pigmentation, hamartomas, breast, GI, pancreatic, and rare GYN/testicular cancers
PTEN Hamartoma Tumor Syndrome	PTEN	Intestinal hamartomas, glycogen acanthosis, skin lesions, macrocephaly, breast, thyroid, renal,endometrial cancers, and CRC
Juvenile Polyposis Syndrome	BMPR1A, SMAD4	Hamartomas, gastric and colon cancer, SMAD4 –HHT overlap

** Autosomal recessive*

Colon Cancer Risk Assessment Tool

Patient who answers yes to any question should have more comprehensive family history evaluation

- 1. Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?
  - Colon or rectal cancer
  - Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain
- 2. Have you had any of the following conditions diagnosed before age 50 years?
  - Colon or rectal cancer
  - Colon or rectal polyps
- 3. Do you have three or more relatives with a history of colon or rectal cancer?
  - This includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins)

Personal and Family History of GI and GYN Cancer

Any (+) Answer Suggests Considering Genetic Testing

CANCER (CA) History & Age	None	You	Sibling/Children (#)	Mother/Mother's Side (#)		Father/Father's Side (#)		Diagnosis age	Living?
COLON or UTERUS CA </= 49									
>/= 3 COLON and/or UTERUS CA same side of family, any age									
>/= 10 COLON ADENOMAS over lifetime									
PANCREAS CA at any age									
OVARIAN CA any age									
BREAST CA </= 49									
Ashkenazi Jewish Heritage with BREAST CA any age									
MALE BREAST CA any age									
>/= 3 BREAST and/or PROSTATE CA same side of family, any age									
COLON or UTERINE CA </= 64									
BREAST CA </= 50									

1st degree relative: Parents, siblings, children
2nd degree relatives: Grandparents, aunts/uncles, nieces/nephews

Offered Genetic Testing: __Yes; __No
__Accepted; __Declined

Which Individuals Should Undergo Multi-Gene Panel Testing for Evaluation of Hereditary CRC/Polyposis

- CRC at age < 50 yrs regardless of MSI status
- Multiple primary Lynch Syndrome cancers (endometrial, gastric, ovarian, pancreatic, ureteral, renal pelvis, biliary, small bowel, or brain tumor, sebaceous gland adenoma or keratoacanthoma).
- CRC and > 1 FDR with CRC or endometrial cancer
- PREMM5 score > 2.5%
- MMRpro or MMR predict score > 5%
- MMR deficient CRC, not due to MLH1 promoter methylation
- Patients meeting other genetic testing criteria
- > 10 cumulative colorectal adenomas
- > 3 cumulative GI hamartomatous polyps

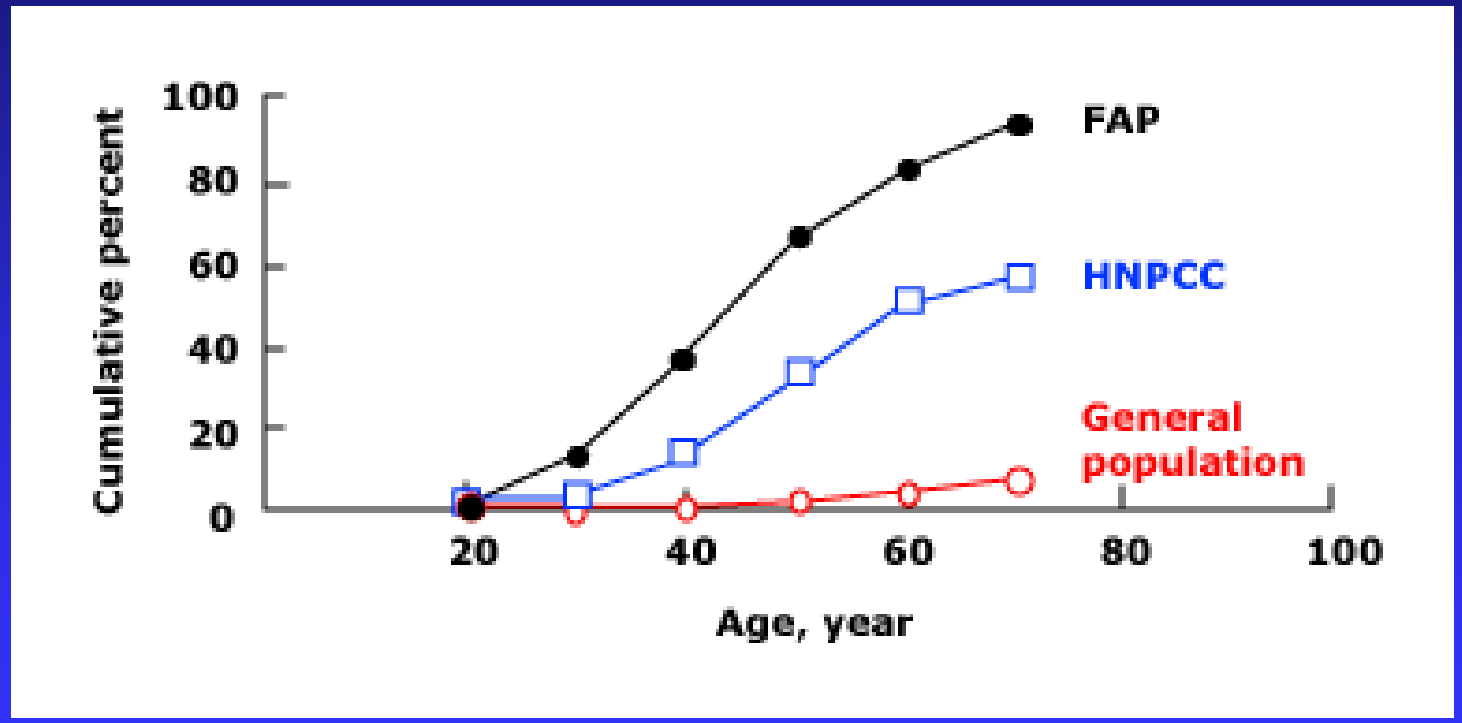
Heald B, et al. Familial Cancer (2020) 19:223–239

Informed Consent for Cancer Genetic Testing

Components of a proper informed consent for cancer genetic testing should include:

1. Information on the specific genetic mutation(s) or genomic variant(s) being tested, including whether or not the range of risk associated with the variant will affect medical care.
2. Implications of positive and negative results.
3. Possibility that the test will not be informative.
4. Options for risk estimation without genetic or genomic testing.
5. Risk of passing a genetic variant to children.
6. Technical accuracy of the test, including, where required by law, licensure of the testing laboratory
7. Fees involved in testing and counseling and, for direct to consumer testing, whether the counselor is employed by the testing company.
8. Psychological implications of test results (benefits and risks).
9. Risks and protections against genetic discrimination by employers or insurers.
10. Confidentiality issues, including, for direct-to-consumer testing companies, polices related to privacy and data security.
11. Possible use of DNA testing samples in future research.
12. Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing.
13. Importance of sharing genetic and genomic test results with at-risk relatives so that they may benefit from this information.
14. Plans for follow-up after testing.

Cumulative Incidence of CRC by Age



Lifetime Cumulative Risk of Colon Cancer

Syndrome	Gene	Risk	Average age of diagnosis (years)	References
Sporadic cancer		4.8%	69	SEER(303)
Lynch syndrome	*MLH1/MSH2*	M: 27–74% F: 22–61%	27–60	(30–35,38)
	MSH6	M: 22–69% F: 10–30% M/F: 12%	50–63	(31,36,49,64)
	PMS2	M: 20% F: 15%	47–66	(37)
Familial adenomatous polyposis (FAP)	*APC*	100%	38–41	(81,123,126,316)
Attenuated FAP	*APC*	69%	54–58	(88,90,126,317–319)
MUTYH-associated polyposis	*MUTYH*	43–100%	48–50	(109,126,134,135,319)
Juvenile polyposis	*SMAD4* *BMPR1A*	38–68%	34–44	(126,220)(320–323)
Peutz–Jeghers syndrome	*STK11*	39%	42–46	(126,196,197)
Cowden syndrome	*PTEN*	9–16%	44–48	(224,235,236,324)
Serrated polyposis syndrome	Not known	~>50%	48	(243,254)

F, female; M, male.

Indicators for Evaluation of Familial Colon Cancer

- CRC or Endometrial Ca before age 50
- CRC younger than 60 with “microsatellite instability high” (MSI-H) histology
  - Tumor-infiltrating lymphocytes
  - Crohn-like lymphocytic reaction
  - Mucinous or signet ring cell differentiation
  - Medullary growth pattern
- Multiple close family members with CRC or other Lynch S cancers
  - Endometrial, Ovarian, Gastric, Small bowel, Brain, Hepato-biliary, Upper Uro-epithelial, Sebaceous gland, or Pancreatic cancer.

Indicators for Evaluation of Familial Colon Cancer

- Multiple primary CRC or other Lynch S cancers
  - Endometrial, Ovarian, Gastric, Small bowel, Brain, Hepato-biliary, Upper Uro-epithelial, Sebaceous gland, or Pancreatic cancer.
- Multiple cumulative GI polyps
  - > 10 colorectal adenomas
  - > 20 colonic serrated polyps (large > 1 cm proximal hyperplastic polyps are likely serrated polyps)
  - 5 or more serrated polyps in the proximal colon, with 2 of them larger than 1 cm
  - 5 or more Hamartomatous GI polyps or any Peutz-Jeghers GI polyp.
- Member of family with confirmed CRC syndrome

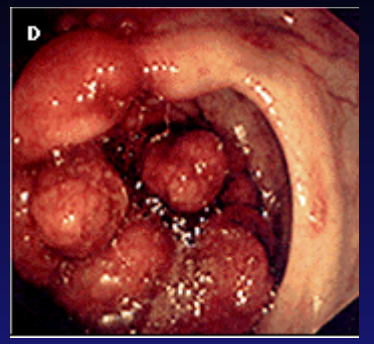
When and how to do MSI Testing

- When:
  - CRC
  - Proximal adenoma > 9 mm
  - Adenoma in < age 40
  - Adenoma or CRC in person with Fam Hx suspicious for HNPCC
- How:
  - Biopsy target lesion (polyp or cancer) and Normal Tissue.
  - IHC (Immuno Hystochem)
- If tissue suggest Lynch S
  - Peripheral blood for germline mutation MLH1, MSH2, MSH6, PMS2 and EPCAM

Adenoma Size	MSI-H	Abnormal IHC
< 5 mm	32%	38%
5-9 mm	29%	57%
>/= 10 mm	100%	100%

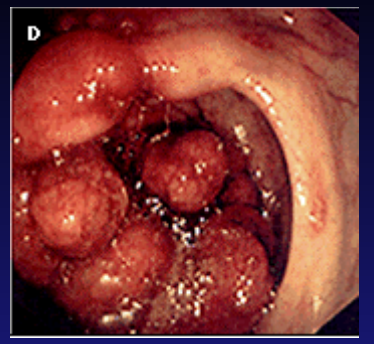
Non-Polyposis Colorectal Cancer Syndromes

HNPCC



- Autosomal dominant, 80% penetrance
- Accounts for 3% of all CRC cases, and 3% Endometrial Ca
- Caused by germ-line mutation in 1 of 6 mismatch repair genes:
  - hMSH2 (41%),
  - hMLH1 (37%),
  - hMSH6 (in 13%),
  - hPMS2 (9%),
  - hPMS1, and hMLH3 (all rare)
- Usually due to germline **mutation in one allele** of a MMR gene and the **second allele is inactivated** somatically by mutation, loss of heterozygosity, or epigenetic silencing by promoter hypermethylation.

HNPCC



- Mean age for CRC development is 44 with some patients presenting in their 20s
- Predominantly right colon involvement
- Adenoma-Carcinoma sequence in 3 years (vs 10-15 y).
- Tumors show microsatellite instability (MSI)
  - MSI is not specific for Lynch syndrome, and approximately 15 percent of sporadic colorectal cancers also demonstrate MSI
- Genetic Counseling is recommended.
- CRC Screening: Colonoscopy q 1-2 y
- Screening beginning Age: 20-25

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Revised Amsterdam Criteria; Gastroenterology 1999; 116: 1453

- Al least 3 relatives with HNPCC-associated Cancer
  - Lynch Syndrome tumors: endometrial, gastric, ovarian, pancreatic, ureteral, renal pelvis, biliary, small bowel, or brain tumor, sebaceous gland adenoma or keratoacanthoma.
- One should be 1st degree relative of the other two.
- At least two successive generations are affected.
- At least one diagnosed before age 50.
- Tumors verified by Pathological Examination.
- Familial Adenomatous Polyposis excluded in CRC cases.

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Revised Bethesda Guidelines

- At least one of the following:
  - CRC diagnosed before age 50.
  - Presence of synchronous CRC, or metachronous CRC, or CRC with other Lynch S associated tumor, all regardless of age.
    - Lynch Syndrome tumors: endometrial, gastric, ovarian, pancreatic, ureteral, renal pelvis, biliary, small bowel, or brain tumor, sebaceous gland adenoma or keratoacanthoma.
  - CRC before age 60, with MSI-H histology
    - tumor-infiltrating lymphocytes, or
    - Crohn-like lymphocytic reaction, or
    - mucinous/signet cell differentiation, or
    - medullary growth pattern)
  - CRC in individual with at least one 1st-degree relative with a Lynch S associated tumor with at least one of the cancers before age 50.
  - CRC in individual with 2 or more 1st- degree or 2nd-degree relatives with Lynch S associated tumors, regardless of age.

Prediction Models for Lynch Syndrome

- MMRpredict model:
  - Sensitivity and Specificity: 94 & 91%
- MMRpro model:
  - Better discriminatory ability compared with the Bethesda guidelines.
- PREMM model:
  - Sensitivity & Specificity: 90 and 67%

Most Effective Strategy for Detection of HNPCC

- Analysis of colorectal tumors for:
  - MMR proteins (MLH1, MSH2, MSH6, and PMS2) showing loss of staining indicating presence of mutation,
  - followed by testing for mutation of BRAF gene:
    - BRAF gene mutation not be present in HNPCC
    - BRAF gene mutation present in sporadic tumors.
- Diagnosis is confirmed by peripheral blood genetic testing for germline mutations in MLH1, MSH2, MSH6, PMS2 and EPCAM genes.
  - If pathogenic gene mutation is found then the result can be used to test other family members and confirms diagnosis
  - Negative results do not rule out diagnosis; use clinical judgement.

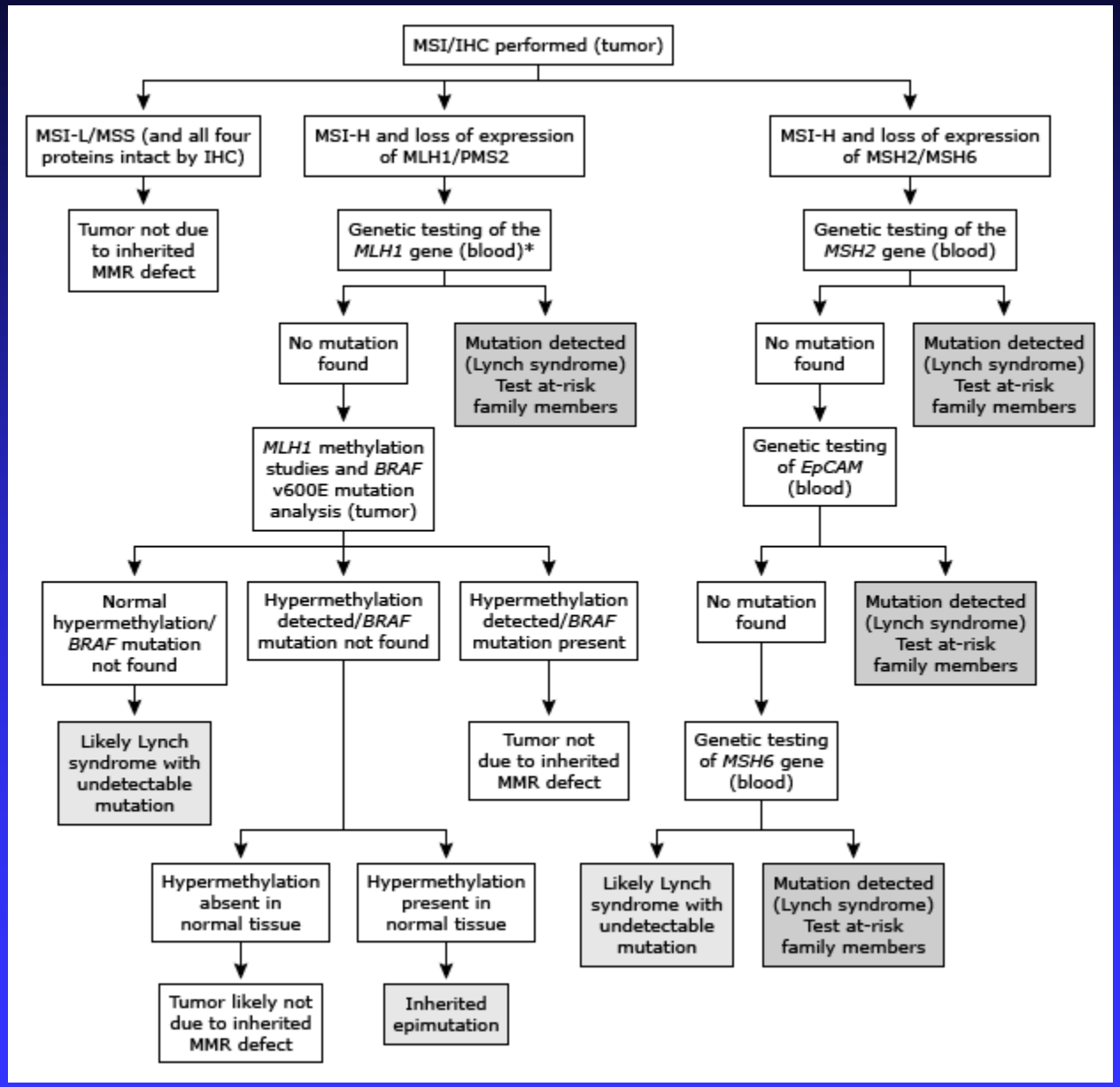
Interpretation of immunohistochemistry results for mismatch repair genes

Result	Possible interpretation	Explanation/comments	Next steps to consider
Absence of MLH1 only (rare occurrence)	1. MLH1 germline mutation	Epigenetic silencing of the MLH1 gene occurs through hypermethylation of the MLH1 promoter	MLH1 germline genetic testing or MLH1 methylation +/- BRAF V600E studies
	2. Hypermethylation of MLH1 promoter		Genetic testing for constitutional MLH1 hypermethylation
Absence of both MLH1 and PMS2	1. MLH1 germline mutation	MLH1 and PMS2 proteins form a heterodimer. Therefore, PMS2 staining is often absent as a result of a MLH1 mutation.	MLH1 germline genetic testing or MLH1 methylation +/- BRAF V600E studies
	2. Hypermethylation of MLH1 promoter	PMS2 germline mutations when tumors show loss of both MLH1 and PMS2 proteins are rare[1,2]	Genetic testing for constitutional MLH1 hypermethylation
Absence of PMS2 only	1. PMS2 germline mutation	MLH1 protein has dimer partners other than PMS2; therefore, germline mutations in PMS2 may not necessarily cause loss of staining for MLH1	PMS2 germline genetic testing
	2. MLH1 germline mutation	MLH1 germline mutations have been identified when tumors show loss of staining for PMS2 only[3,4]	MLH1 germline genetic testing if PMS2 testing does not identify a germline mutation
Absence of MSH2 only (rare occurrence)	1. MSH2 germline mutation	Strong likelihood of a MSH2 or EPCAM mutation	MSH2 germline genetic testing
	2. EPCAM germline mutation	Other epigenetic events that result in silencing of MSH2 are undetermined	EPCAM deletion studies if MSH2 testing does not identify a germline mutation

Interpretation of immunohistochemistry results for mismatch repair genes

Result	Possible interpretation	Explanation/comments	Next steps to consider
Absence of both MSH2 and MSH6	1. MSH2 germline mutation	MSH2 and MSH6 proteins form a heterodimer; therefore, MSH6 staining is often absent as a result of MSH2 mutation.	MSH2 germline genetic testing
	2. EPCAM germline mutation		EPCAM +/- MSH6 germline genetic testing if MSH2 testing does not identify a germline mutation
	3. MSH6 mutation		
Absence of MSH6 only	1. MSH6 germline mutation	MSH2 protein has dimer partners other than MSH6; therefore, germline mutations in MSH6 tend to cause loss of staining for MSH6 only	MSH6 germline genetic testing
	2. MSH2 germline mutation		MSH2 germline genetic testing if MSH6 testing does not identify a germline mutation
All proteins exhibit normal staining	1. No Lynch syndrome	Normal IHC results do not exclude Lynch syndrome; missense mutation could result in intact, but nonfunctional MMR protein	Refer to MSI results +/- family history to guide further evaluation
	2. Possible missense germline mutation in MLH1, MSH2, MSH6 or PMS2		

Testing Algorithm for Possible Lynch



HNPCC Lifetime Cancer Risk

Colorectal cancer	82%
Endometrial cancer	43%-60%
Gastric cancer	13%-19%
Ovarian cancer	9%-12%
Urinary tract cancer	4%-10%
CNS (glioblastoma = Turcot S.)	3.7%
Renal cell adenoCA	3.3%
Biliary tract and gall bladder CA	2%-18%
Small bowel cancer	1%-4%

- **Screening for extracolonic tumors is recommended.**

Lifetime Cancer Risk in Lynch Syndrome

Cancer site	MLH1		MSH2		MSH6		PMS2	
	Men	Women	Men	Women	Men	Women	Men	Women
Any Lynch cancer	**59%**	**80%**	**71%**	**75%**	**31%**	**71%**	-	-
Colorectal	34 to 47%	36 to 45%	37 to 47%	33 to 37%	14 to 22%	10 to 26%	19 to 20%	11 to 15%
Endometrial	NA	18 to 60%	NA	21 to 60%	NA	16 to 71%	NA	13 to 24%
Ovarian	NA	11 to 20%	NA	15 to 24%	NA	0 to 1%	NA	0%
Urinary tract	1.2%	3%	8%	10%	0.7%		-	
Gastric	20%	8%	2%	9%	-		-	
Small bowel	0.4%*		1.1%*		-		-	
Biliary/pancreatic	1.9%*		0.02%*		-		-	
Brain tumors (gliomas)	1.7%*		2.5%*		-		-	

HNPCC Screening for Extracolonic Tumors

- Endometrial & Ovarian Ca:
  - Pelvic exam, endometrial aspirate, & transvaginal U/S every year after age 25.
  - Discuss prophylactic hysterectomy + salpingo-oophorectomy at age 35 or end of childbearing.
- Renal pelvis & Ureter Ca:
  - Renal U/S every year after age 25
  - U/A + cytology every year after age 25.
- Skin Ca:
  - Annual skin surveillance for sebaceous carcinoma.
- Gastric & Small bowel Ca:
  - EGD q 1-2 y after age 30.
- Other:
  - Annual physical exam and Review of systems for related tumors.
  - Avoid smoking (increases CRC Risk)

Muir-Torre and Turcot in Lynch

- **Muir-Torre Syndrome:** sebaceous tumors and cutaneous keratoacanthomas, in addition to cancers associated with Lynch syndrome.
  - Sebaceous tumors have been reported in carriers of all four MMR genes, but individuals with *MSH2* mutations are particularly predisposed.
- **Turcot syndrome:** Association of familial CRC with brain tumors. In Lynch syndrome are usually **gliomas** (versus majority of FAP-associated brain tumors are medulloblastomas)

Familial Colorectal Cancer Type X

- Fulfill criteria of Amsterdam I, but DO NOT have Microsatellite Instability (MSI).
- Have increased risk of CRC but less than those with MSI-H.
- Do not have increased risk for other cancers.

Polyposis Colo-Rectal Cancer Syndromes

Adenomatous and Serrated

Familial Adenomatous Polyposis (FAP)

- Autosomal dominant
- Mutation in “adenomatous polyposis coli” gene (APC) in chromosome 5q21.
- APC – is a tumor suppressor gene
- Prevalence of FAP vary from 1 in 6,850 to 1 in 31,250 live births (2.29 to 3.2 cases per 100,000 individuals)
- De novo mutation found in 25-30% of FAP (20% of may have mosaicism mimicking “de novo” mutation).
- Accounts of < 1% of colon cancer in the US

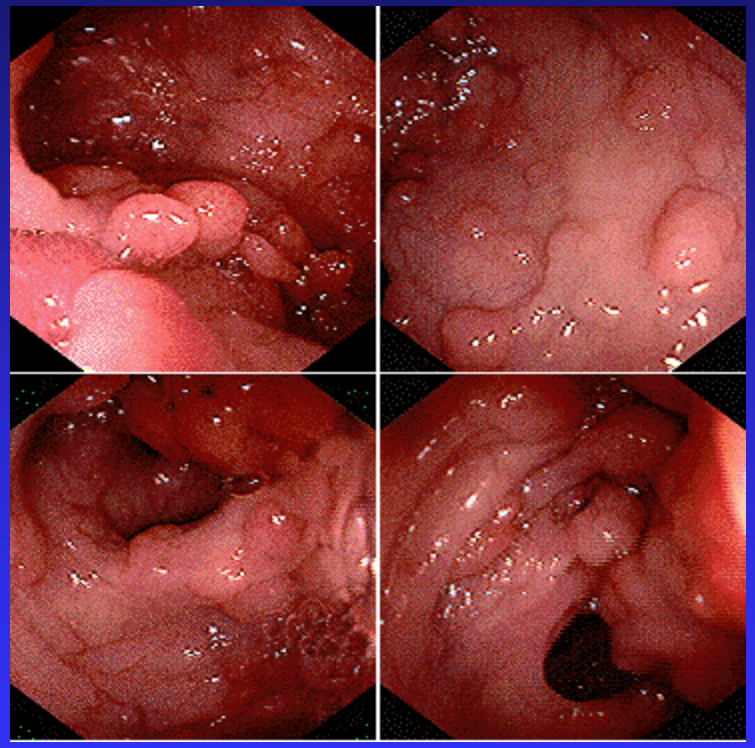
Familial Adenomatous Polyposis (FAP)

- Diagnosis – > 100 adenomatous colorectal polyps
  - 10-99 polyps is “Attenuated FAP” (AFAP)
- APC mutation in proband confirms diagnosis and allows to identify relatives.
- Almost always involves rectosigmoid
- Average age of adenoma appearance = 16 yrs
- Average age of colon cancer = 39 yrs
- Genetic Counseling is recommended.
- CRC Screening: colonoscopy q 1-2 y after age 10-12; once adenomas are found, q 1y until colectomy.

Familial Adenomatous Polyposis (FAP)

- Colectomy:
  - When > 20 adenomas are found.
  - When adenoma > 1 cm is found.
  - When “advanced histology” develops (villous)
- Treatment:
  - Large number of rectal adenomas: total proctocolectomy with ileal pouch anal anastomosis. May leave 1-2 cm rectal mucosal cuff for air-liquid-solid discrimination.
  - Few rectal adenomas: Colectomy with ileo-rectal anastomosis + annual proctoscopy + sulindac or celecoxib. Up to 33% will need completion proctectomy due to new polyps.

FAP



Attenuated FAP (AFAP)

- Diagnosis: suspect with >10 but < 100 adenomas in person older than 40 y; confirm by finding APC mutation.
- AFAP and MAP represent 10-20% of adults with 10-100 adenomas.
- Average age of adenoma appearance = 44 yrs
- Average age of colon cancer = 56 yrs
- Frequent involvement of proximal colon: needs colonoscopy.
- Infrequent involvement of rectum
- Lifetime risk of colon cancer is 69%
- Mutations in APC gene are close to 5-prime end or 3-prime end of the gene.
- Genetic Counseling is recommended.
- CRC Screening: Colonoscopy q 1-2 y beginning in late teens. Up to 66% will eventually need colectomy with ileo-rectal anastomosis + annual proctoscopy.

FAP- AFAP
Extracolonic involvement

- Duodenal and ampullary carcinoma (4-12%)
- Follicular or papillary thyroid cancer (1-2%)
- Pancreas (2%)
- Childhood hepatoblastoma (1-2%)
- Gastric carcinoma (< 1%)
- CNS tumors (medulloblastoma) (<1%)
- Gastric fundic gland polyps (benign); only severe dysplasia is of concern.
- Duodenal adenomas in > 50% (usually in 2nd and 3rd portion)
- Adenomas in distal small bowel and stomach (usually antrum) (cancer risk lower than for duodenal adenomas)
- Adenomas in gallbladder and bile duct (occasional adenocarcinoma)
- Osteomas (skull and mandibule), Congenital Hypertrophy of Retinal Pigment Epithelium, epidermoid cysts, fibromas, desmoids, and dental abnormalities.
- **Screening for extracolonic tumors is recommended.**

FAP and AFAP
Screening for Extracolonic Tumors

- Papilla of Vater, Duodenal, and Gastric Ca:
  - EGD with end-view & side-view scope at age 25 & repeat every 1-3 years; if lesions are found in papilla of Vater or duodenum, treat and shorten the interval to yearly.
  - EUS of suspicious lesions at the ampulla
  - Remove antral adenomas & Bx large or erythematous fundic polyps to asses for dysplasia.
  - Do Spigelman staging of duodenal adenomatosis. Celecoxib 400 mg BID can decrease duodenal adenomas.
- Thyroid Ca:
  - Palpation of thyroid +/- thyroid U/S each year.
- Hepatoblastoma:
  - Abdominal palpation & AFP every 6 months from birth to age 6.
- Ileal Ca:
  - Regular surveillance of ileal pouch ?

Management by Spigelman Score and Stage in Duodenal Adenomatosis

Polyps	1 Point	2 Points	3 Points
Number	<4	5–20	>20
Size	0–4 mm	5–10 mm	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Spigelman stage	Total points	Frequency of surveillance
	Recommended duodenal surveillance frequency[b]	
0	0	Every 4 years
I	≤4	Every 2–3 years
II	5–6	Every 1–3 years
III	7–8	Every 6–12 months
IV	9–12	Expert surveillance every 3- 6 months
		Surgical evaluation
		Complete mucosectomy or duodenectomy or Whipple procedure if duodenal papilla is involved

[a]Adapted from ref. (154).

[b]Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Colorectal V.1.2014. 2014 National Comprehensive Cancer Network (24) The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK, NCCN, NCCN GUIDELINES, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network.

Staging and Cancer Risk of Duodenal Polyposis

Groves C, GUT 2002;50:636

Stage	Spigelman's Score Points	Cancer Risk
I	1-4	0%
II	5-6	2.3%
III	7-8	2.4%
IV	9-12	36%

FAP and AFAP
Screening for Extracolonic Tumors

- Surgical consultation – for advanced (Spigelman stage IV) duodenal polyposis in an effort to prevent periampullary/duodenal carcinoma.

- Management of high-grade dysplasia in the periampullary region is controversial and must be individualized (surgery/ablative therapy versus more frequent surveillance)

MutYH (MYH) Associated Polyposis

- Autosomal recessive
- Biallelic (homozygous or compound heterozygous) MUTYH mutations; more than 80% at Y179C and G396D
- MYH gene is involved in base excision repair.
- Mimics Attenuated-FAP, with propensity to proximal colon neoplasm.
- Adenomatous polyps predominate, but hyperplastic and serrated polyps are also very common.
- Typically polyps occur in patient in his/her 40s (sometimes earlier).

MutYH (MYH) Associated Polyposis

- **Diagnosis: >10 to > 100 colonic polyps but with no APC mutation. MYH mutation confirms diagnosis and allows family testing.**
- **Sibling have 25% risk of MAP. Parents and children are rarely affected, but should be counseled.**
- **CRC Screening: Colonoscopy q 2-3 years, starting at age 25.**
- **Treatment: Subtotal colectomy for:**
  - **Colon cancer**
  - **Problematic Colonoscopy management**
  - **Large polyps**
  - **Polyps with high grade dysplasia**
- **Genetic Counseling is recommended.**

MAP (MYH associated polyposis) – Extracolonic manifestations

- Gastroduodenal polyps (11%)
- Duodenal polyps (17%)
- Duodenal Ca in 4%
- Bladder cancer
- Ovarian cancer in female carriers
- Skin cancer
- Dental cysts
- Sebaceous gland tumors
- Breast cancer.
- **Screening for extracolonic tumors is recommended (stomach, duodenum & breast).**

MAP
Screening for Extracolonic Tumors

- Duodenal Ca & Gastric polyps:
  - EGD q 1-3 y starting at age 20-25.
- Breast Ca:
  - women should do monthly self-exam,
  - clinical breast exam every 6 months, and
  - annual mammograms.

Serrated Polyposis Syndrome

- Multiple and/or large serrated polyps (including “serrated adenomas” (SA)) in the colon.
- Increased risk for colorectal cancer due to BRAF and/or CIMP (CpG Island Methylator Phenotype) mutation.
- CRC usually in 50s or 60s.
- Life-long risk of CRC is 37-69%.
- Evidence of inheritance is weak (but screening is recommended for 1st degree relatives)
- Diagnosis:
  - At least 5 histologically diagnosed serrated polyps proximal to the sigmoid colon of which 2 are greater than 1 cm, **OR**
  - Any number of serrated polyps proximal to the sigmoid in a patient with a 1st degree relative with hyperplastic polyposis, **OR**
  - More than 20 cumulative serrated polyps of any size distributed throughout the colon

Serrated Polyposis Syndrome

- Colonoscopy q 1 year to remove at least all polyps > 5 mm (ideally remove all polyps independently of size, because CRC may develop in polyps < 5 mm).
  - SA are often slightly elevated, covered by mucus, and pale being difficult to see.
  - Flushing all remnant stool, chromoendoscopy and NBI can help.
- Management. Colonoscopy + Polypectomy. If:
  - a) all polyps > 5 mm can not be removed, or
  - b) High grade dysplasia or multiple adenomas > 6 mm, or
  - c) patient refuses frequent colonoscopies, or
  - d) cancer is detected,
  - THEN patient should have colectomy with ileo-rectal anastomosis.
- First degree relatives should be offered screening colonoscopy at age 10 y earlier than index case.

Gastrointestinal Polyposis Cancer Syndromes

Hamartomatous

Juvenile Polyposis Syndrome (JPS)

- Autosomal dominant Hamartomatous Polyposis.
- Incidence < 1/100,000
- Gene (Chromosome18): mutation in SMAD4 (chromosome 18q21.1), or BMPR1 (chromosome 10q22-23).
  - Cytoplasmic mediator in TGF-β signalling.
  - Found in only 60% of JPS.
  - 25% de-Novo mutations
- May have Hereditary Hemorrhagic Telangiectasia, or congenital defects (only with SMAD4 mutation).
- Diagnosis:
  - more than 5 juvenile polyps in the colon/rectum,
  - multiple JP in the GI tract, or
  - any number of JP with family history of JPS

Juvenile Polyposis Syndrome

- Most symptomatic by age 20
- Risk of colon CA – may be up to 39%.
  - 17-22% by age 35
- Increased risk of Gastric (20-30% lifetime; mean age 58), pancreas & small bowel cancer in 21%.
- Strong association with Hereditary Hemorrhagic Telangiectasia (only with SMAD4).
- Genetic Counseling is recommended.
- CRC Screening: Colonoscopy q 2-3 y beginning with symptoms, or at age 12.
- **Screening for extracolonic tumors is recommended (stomach & small bowel).**

Juvenile Polyposis Syndrome Screening for Extracolonic Tumors

- Gastric & SB polyps and Ca:
  - EGD start at age 12; q 1 y if polyps found; q 3 y if no polyps found
  - SB series or VCE, or Balloon Enteroscopy every 1-3 years (depending on polyp burden), starting at late teenage years
- HHT:
  - Evaluation for clinical evidence of Hereditary Hemorrhagic Telangiectasia if SMAD4 (+) (epistaxis, telangiectasia, visceral lesions, family history) which will prompt evaluation for occult AVMs.

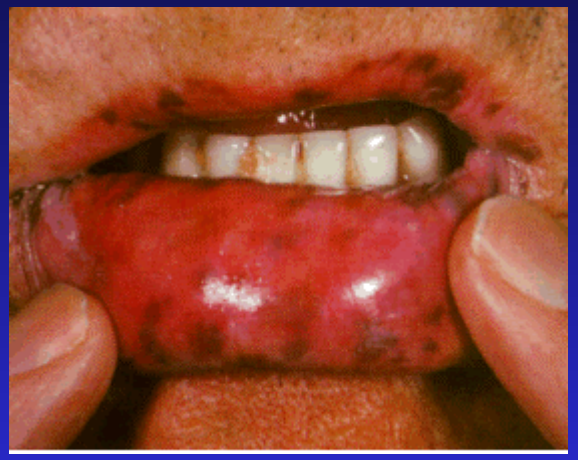
Peutz-Jeghers Syndrome

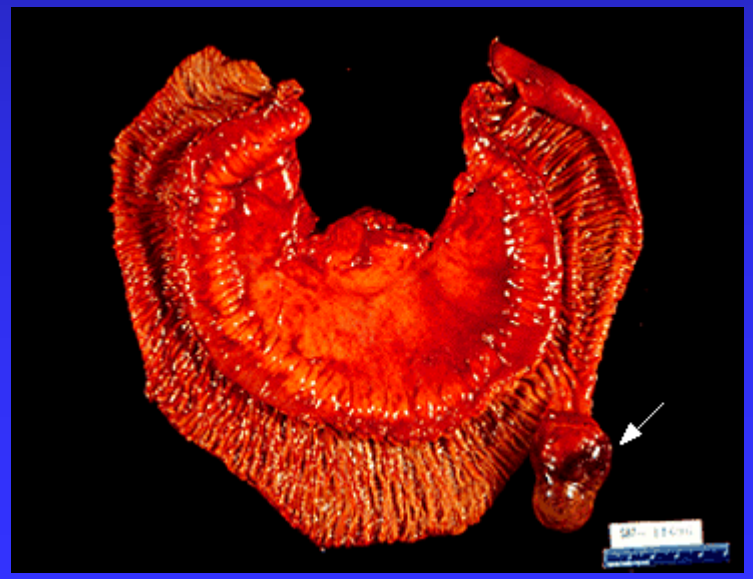
- Autosomal dominant (prevalence: 1/8,000 to 1/200,000)
- Germ line mutation of a gene STK11 (LKB1) on chromosome 19. Gene encodes a serine threonine kinase.
  - high penetrance of over 90 percent by the age of 30 years
  - 10 to 20% have no family history (de novo mutations).
- Pigmented spots on lips and buccal mucosa (> 95%)
- Multiple gastrointestinal hamartomatous polyps
  - small bowel: 65-95% (more in jejunum); colon: 30-60%; stomach: 25-50%)
- Diagnosis with 2 or more of:
  - 2 or more PJ polyps in GI tract
  - Typical mucocutaneous pigmentation
  - Family history of PJS.

Peutz-Jeghers Syndrome

- GI cancer risk is via adenomatous change within hamartoma (colon, stomach & SB).
- Lifetime risk of CRC is 39%.
- Genetic Counseling is recommended.
- Screening for extracolonic tumors is recommended.
- Screening: Colonoscopy + EGD + VCE (or MR Enterography) q 2-3 y beginning with symptoms, or at age 8 (whichever is first), with removal of polyps > 0.5 cm

Peutz-Jeghers Syndrome





Peutz-Jeghers Syndrome
Lifetime Cancer Risk

Breast	54%
Colon	39%
Pancreas	36%
Stomach	29%
Ovary	21%
Lung	15%
Small intestine	13%
Uterus	9%
Esophagus	0.5%
Testicular Sertoli tumor	9% in males

Peutz-Jeghers
Screening for Extracolonic Tumors

- Birth to age 10:
  - a) Males:
    - H&P and routine blood work annually,
    - U/S of testicles every 2 years until age 10.
  - b) Females:
    - H&P and routine blood work annually.
- From age 8:
  - a) Males:
    - EGD q 2-3 y
    - MR Enterography or Wireless Capsule Endoscopy every 2-3 years.
    - Annual testicular exam / U/S of testicles + observation for feminizing changes.
  - b) Females:
    - EGD q 2-3 y+
    - MR Enterography or Wireless Capsule Endoscopy every 2-3 years.

Peutz-Jeghers
Screening for Extracolonic Tumors

- Add from age 18 for females:
  - Annual pelvic exam,
  - Annual Pap smear, and
  - Annual transvaginal ultrasound.
- Add from age 25:
  - a) Males:
    - EUS or MRCP of pancreas every 1-2 years.
  - b) Females:
    - EUS or MRCP of pancreas every 1-2 years.
    - Clinical breast exam every 6 months.
    - Annual Mammogram and Breast MRI.

PTEN Hamartomatous Tumor Syndrome (PHTS)

- Includes Cowden Syndrome (CS) and Bannayan-Riley-Ruvalcaba Syndrome (BRRS).
- Autosomal dominant with high-penetrance.
- Caused by germline mutation in “phosphatase and tensin homolog” gene (PTEN).
- Can have various polyps: hamartomas, hyperplastic, adenomas, ganglioneuromas, and inflammatory.
- Increased risk for CRC, as well as breast, thyroid, endometrium, renal, and melanoma.
- Screening starting at age 18, or 5 years before index case, for:
  - Yearly skin and thyroid exam (ultrasound).
  - Breast Mammogram + MRI) and endometrial cancer screening (TVUS + endometrial Bx) q year starting at 30.
  - Colonoscopy at age 35, then by findings (at least q 5 y).
  - Renal U/S starting at 40, q 2 y

Revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria

- Operational diagnosis in an individual (either of the following):
  - 1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
  - 2. Two major and three minor criteria.
- Operational diagnosis in a family where one individual meets revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* mutation:
  - 1. Any two major criteria with or without minor criteria; or
  - 2. One major and two minor criteria; or
  - 3. Three minor criteria.

Revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria

MAJOR CRITERIA	MINOR CRITERIA
Breast cancer	Autism spectrum disorder
Endometrial cancer (epithelial)	Colon cancer
Thyroid cancer (follicular)	Esophageal glycogenic acanthosis (≥3)
Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)	Lipomas (≥3)
Lhermitte-Duclos disease (adult)	Mental retardation (ie, IQ ≤75)
Macrocephaly (≥97 percentile: 58 cm for females, 60 cm for males)	Renal cell carcinoma
Macular pigmentation of the glans penis	Testicular lipomatosis
Multiple mucocutaneous lesions (any of the following): -Multiple trichilemmomas (≥3, at least one biopsy proven) -Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules) -Mucocutaneous neuromas (≥3) -Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed	Thyroid cancer (papillary or follicular variant of papillary)
	Thyroid structural lesions (eg, adenoma, multinodular goiter)
	Vascular anomalies (including multiple intracranial developmental venous anomalies)

Effect of Inherited Disorders on Onset & Frequency of Screening Colonoscopy

Category	Start age (the lesser)	Interval
Serrated Polyposis Syndrome	First degree relative: 10 y younger than index case	1 y (to remove all polyps > 5 mm)
Peutz-Jeghers Syndrome	With symptoms or late teens (whichever is first)	2-3 years
Juvenile Polyposis Syndrome	With symptoms or late teens (whichever is first)	2-3 years
HNPCC (gene carrier or risk) **(Muir-Torre & Turcot w glioblastoma)**	20, or [10 y before "index"] whichever is first	2 years; q 1 y after 40
MYH associated Adenomatous Polyposis (MAP) [> 15 adenomas]	25	2-3 year
FAP/Gardner/Turcot with medulloblastoma/Attenuated APC	10	Yearly colonoscopy

Summary

- CRC is very common and highly preventable.
- Patients should be stratified for risk of CRC at ages 20 & 40.
- Patients with “average risk” for CRC should start screening at age 50, preferably with “high quality” colonoscopy at 10-year intervals (with shorter follow-up intervals if adenoma and/or carcinoma is found).
- Patients with “increased-risk” or “high-risk” for CRC should have screening with “high quality” colonoscopy, starting at ages and followed at intervals commensurate to the expected onset and severity of the risk.

Other Hereditary Gastric and Pancreatic Cancers

Inherited Gastric Cancer

- Four histological categories include: (1) glandular/Intestinal (74%), (2) mixed intestinal/diffuse (16%), (3) border foveal hyperplasia, and (4) solid/undifferentiated.
- 5%–10% of gastric cancers are associated with strong familial clustering and can be attributed to genetic factors

Comparison of hereditary cancer syndromes.

Syndromes	Genes	Gastric cancer risk, %	Inheritance	Reference
Hereditary diffuse gastric cancer syndrome (HDGC)	*CDH1*	56–70	Autosomal dominant	[43]
Peutz-Jeghers syndrome	*STK11*	29	Autosomal dominant	[32]
Juvenile polyposis	*SMAD4, BMPR1A*	21	Autosomal dominant	[32]
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	1-13	Autosomal dominant	[32]
Li-Fraumeni syndrome	*TP53*	2.8	Autosomal dominant	[49]
Familial adenomatous polyposis	*APC*	1-2	Autosomal dominant	[32]
Hereditary breast and ovarian cancer syndrome (HBOC)	*BRCA1, BRCA2*	Undetermined	Autosomal dominant	
Gastric adenocarcinoma and proximal polyposis syndrome	Unknown implicated gene	Undetermined	Autosomal dominant	
MYH-associated polyposis	*MYH*	Undetermined	Autosomal recessive	

Hereditary Diffuse Gastric Cancer

- Hereditary Diffuse Gastric Cancer (HDGC):
  - Autosomal Dominant mutation of Germline E-cadherin CDH1, located on chromosome 16q22.1
  - 1%–3% gastric cancers or 1/3 of diffuse or signet cell familial associated gastric cancers.
- Diagnostic criteria for HDGC includes:
  - at least two cases of diffuse gastric cancer in first- or second-degree relatives (one of which occurs prior to age 50),
  - three documented cases of diffuse gastric cancer regardless of age,
  - diffuse gastric cancer in individuals less than 40 years of age without a family history, or
  - individuals and families with diagnoses of both diffuse gastric cancer and lobular breast cancer in which one of the cases is < 50 years of age.
- Also consider CDH1 Testing in:
  - Bilateral lobular breast cancer under age 50 years or the presence of multiple close relatives with lobular breast cancer (at least two cases diagnosed under 50 years).
  - Individuals with a personal or family history of cleft lip/cleft palate and diffuse gastric cancer.

Hereditary Diffuse Gastric Cancer

- High cancer penetrance for heterozygotes but 20%–30% of individuals with pathogenic germline CDH1 mutations may never develop invasive gastric cancer
- Significant mortality if not diagnosed early (occurs as early as age 14),
- Genetic counseling and testing should occur early, with consideration for prophylactic surgery
  - Screening EGD regularly fails to identify diffuse gastric carcinoma as these lesions spread submucosally as single cells or clustered islands of cells.
- Total gastrectomy with D1 node dissection is offered to CDH1 mutation carriers from HDGC families at age 5 years younger than the youngest age at which a family member developed clinical symptoms of HDGC.
- Women with HDGC have a 42% risk for lobular breast cancer by age 80 years; monthly breast exam + annual mammogram/breast MRI starting at age 25.
- Management of individuals with CDH1 mutation but no family history is unclear.

Hereditary Diffuse Gastric Cancer
Additional Genetic Variants

I. Petrovchich, J.M. Ford / Seminars in Oncology 43 (2016) 554–559

Newly identified variants.

Gene	Mutation	Mutation type	References
CTNNA1	c.76delGA	Nonsense	[13,50]
	c.211A→AT	Frameshift	
	c.385C→T	Nonsense	
MAP3K6	c.598G→T	Missense	[13,50]
	c.620T→G	Missense	
	c.2837C→T	Silent	
	c.2872C→A	Missense	
	c.2544delC	Nonsense	
INSR	c.3937G→A	Missense	[50]
FBXO24	c.242G→C	Missense	[50]
DOT1L	c.3437C→T	Missense	[50]
PRSS1	c.256C→T	Nonsense	[13]
MSR1	c.877C→T	Nonsense	[13]

Li-Fraumeni syndrome (LFS)

- Autosomal dominant inherited cancer syndrome characterized by multiple primary tumors of diverse phenotypes
- Germline TP53 mutations (located on Chr 17p13.1) in 70%
- In gastric carcinoma, mutations in exons 5–8 of the 11-exon TP53 gene, which lead to a compromised DNA-binding domain and extremely high penetrance, have overall cancer risk approaching 100% in female carriers and 73% in male carriers.
- Most common tumors are sarcomas, breast carcinomas, brain tumors, leukemias, and adrenal cortical carcinomas,
  - gastric carcinomas in 1.8%–4.9% of LFS carriers (22.6% of LFS families have at least one member with gastric carcinoma, as early as age 12)
- Periodic screening gastroscopy of carriers with at least one family member affected by gastric cancer should be considered; start at early age (12 years?)

Hereditary Breast and Ovarian Cancer syndrome (HBOC)

- Autosomal recessive syndrome caused by a germline mutation in either BRCA1 (located on Chr 17q.21.31) or BRCA2 (located on 13q.13.1).
- Prevalence of 1/400 in the general population and up to 1/40 in select groups with founder mutations (Ashkenazi Jewish ancestry)
- CANCER RISK:
  - Breast cancer (57% for BRCA1 and 49% for BRCA2) and ovarian cancer (40% for BRCA1 and 18% for BRCA2)
  - Gastric cancer before the age of 70 is twice as common in BRCA1/2 carriers as it is in the general population
  - 2-9 fold increase in Pancreatic Cancer
- Currently, there are no screening guidelines for the surveillance of gastric carcinoma in BRCA carriers

Gastric Adenocarcinoma and proximal Polyposis Syndrome (GAPPS)

- Autosomal dominant disorder with incomplete penetrance and a currently unknown etiology
- Diagnostic criteria:
  - >100 gastric polyps in the index case or >/= 30 polyps in a first-degree relative of a known case,
  - polyps restricted to the body and fundus of the stomach,
  - absence of colorectal or duodenal polyposis,
  - morphologically confirmed fundic gland polyps with areas of dysplasia or carcinoma, and
  - autosomal dominant inheritance.
- Management should be based on personal and family history, and developed on a case-by-case basis.
- Presence of gastric polyposis presents potential difficulties with endoscopic surveillance, and total gastrectomy may be considered

Familial Pancreatic Cancer

Syndrome	Relative risk of pancreatic cancer	Gene	References
Familial atypical multiple melanoma and mole (FAMMM)	13- to 39-fold	*CDKN2A*	(265–267)
Familial breast and ovarian	2-fold3- to 9-fold	*BRCA1BRCA2*	(268)(269,270)
Fanconi anemia, breast CA	Unknown	*PALB2*	
Familial adenomatous polyposis (FAP)	5-fold	*APC*	(334)
Lynch	9- to 11-fold	*MLH1, MSH2MSH6, PMS2*	(71,362)
Peutz–Jeghers syndrome	Up to 132-fold	*STK11/LKB1*	(197)
Li–Fraumeni	Unknown	*p53*	
Hereditary pancreatitis	53-fold	*PRSS1*	(264)
Ataxia–telangiectasia	3-fold	*ATM*	(272)
Familial pancreatic cancer:			
1 Or 2 first-degree relatives	4- to 7-fold	See **Table 13**	(276,277)
≥3 First-degree relatives	17- to 32-fold	Majority unknown	

Increasing Colonoscopy Screening

Increasing Colonoscopy Screening

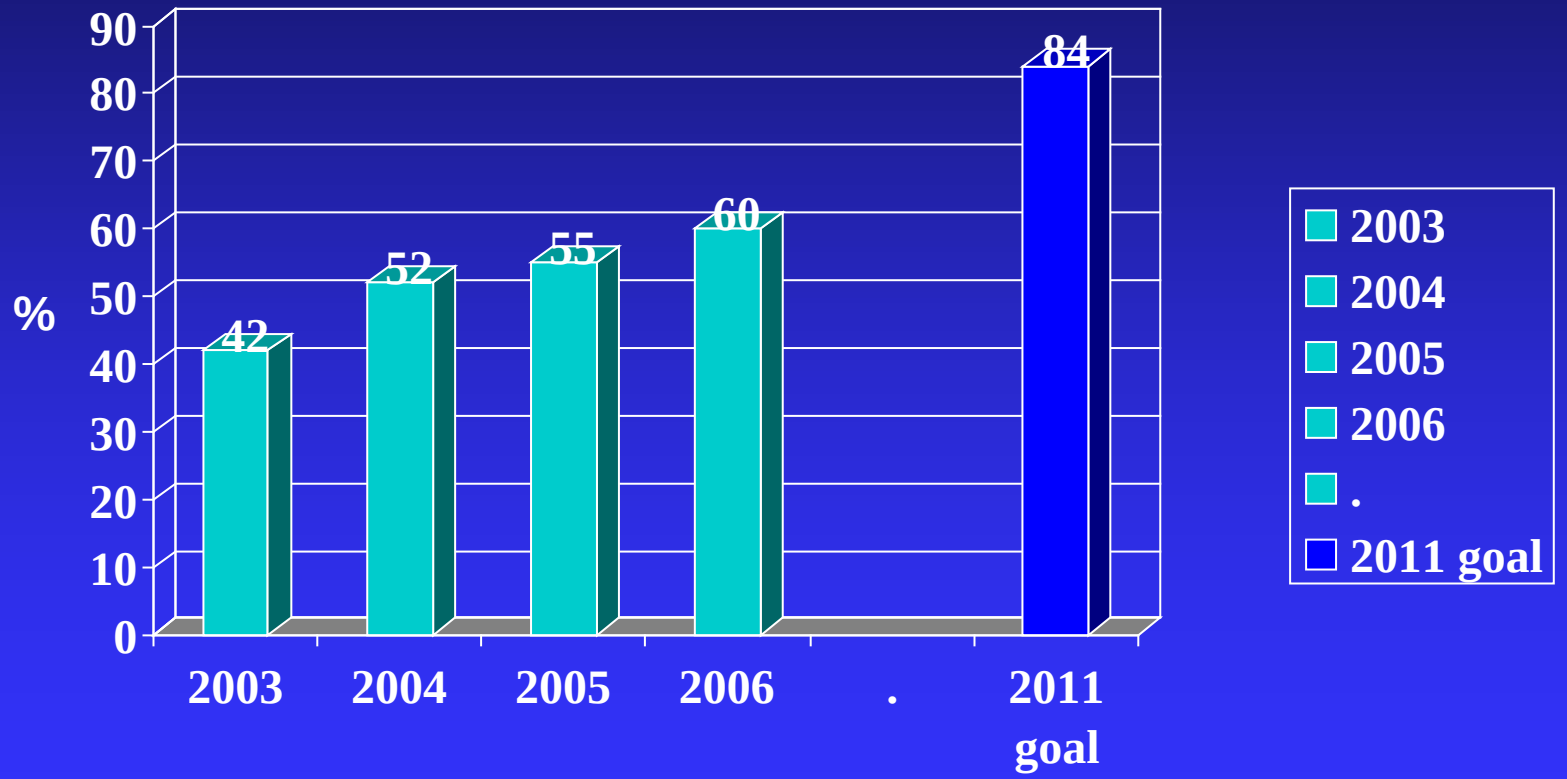
Best Practices

New York City Experience

- Promote routine colonoscopy for outpatients age 50 or older
- Use “direct endoscopy referral system”
- Use “Navigators” to decrease “no-show” and “poor-prep” rates
- Implement “triage”: screen higher risk first
- Use a “social worker” to assist “self-pay” patients to see if
  - they qualify for Medicare/Medicaid (20%), or
  - to arrange for a “income-based sliding-scale fee” with a “payment-plan”
- Identify patients likely to slow “throughput”, and schedule them late in the day.

Effect of “Best Practices” in Rate of CRC Screening

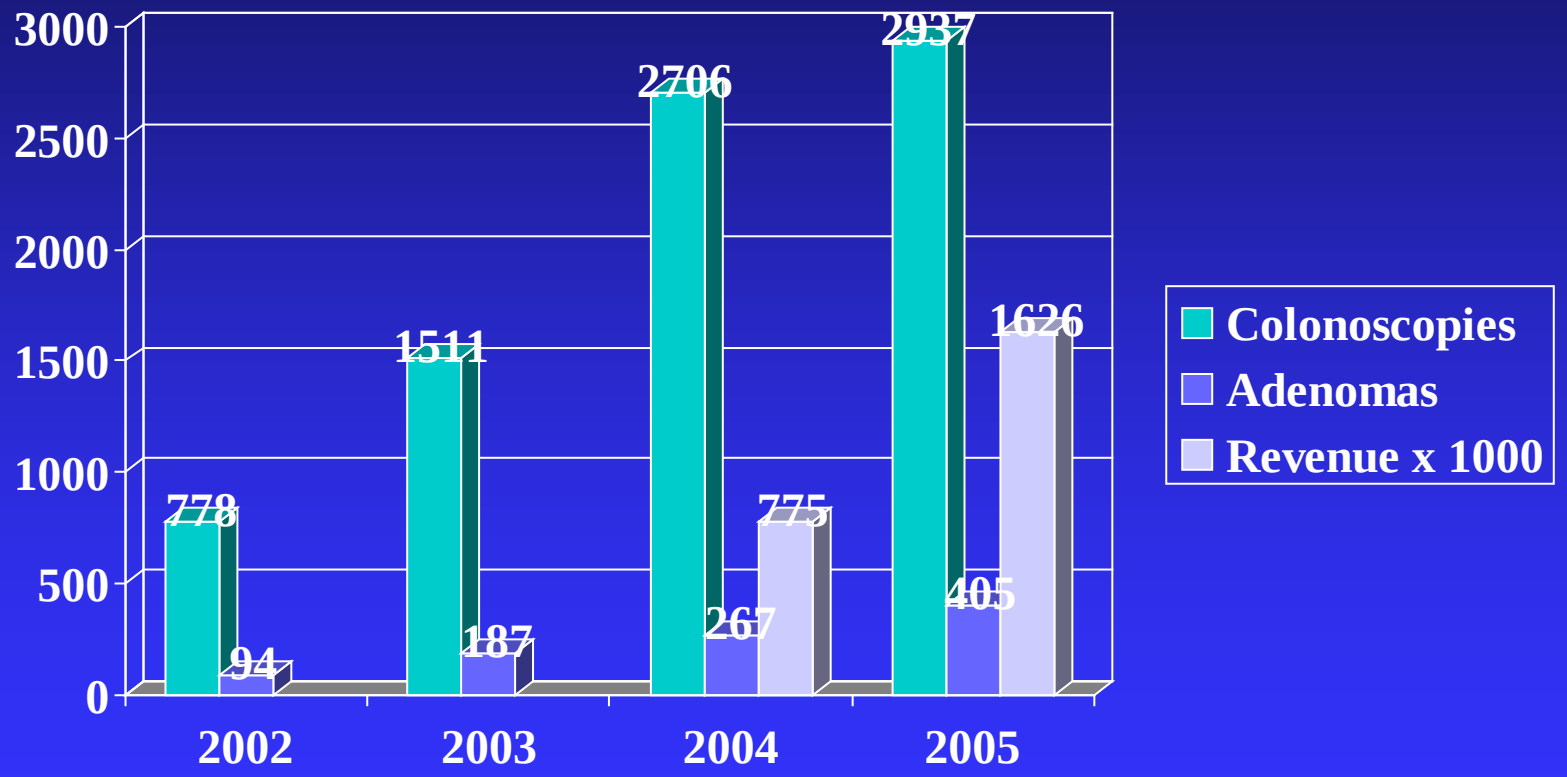
New York City Community Health Survey



% New Yorkers 50+ who had colonoscopy in last 10 years

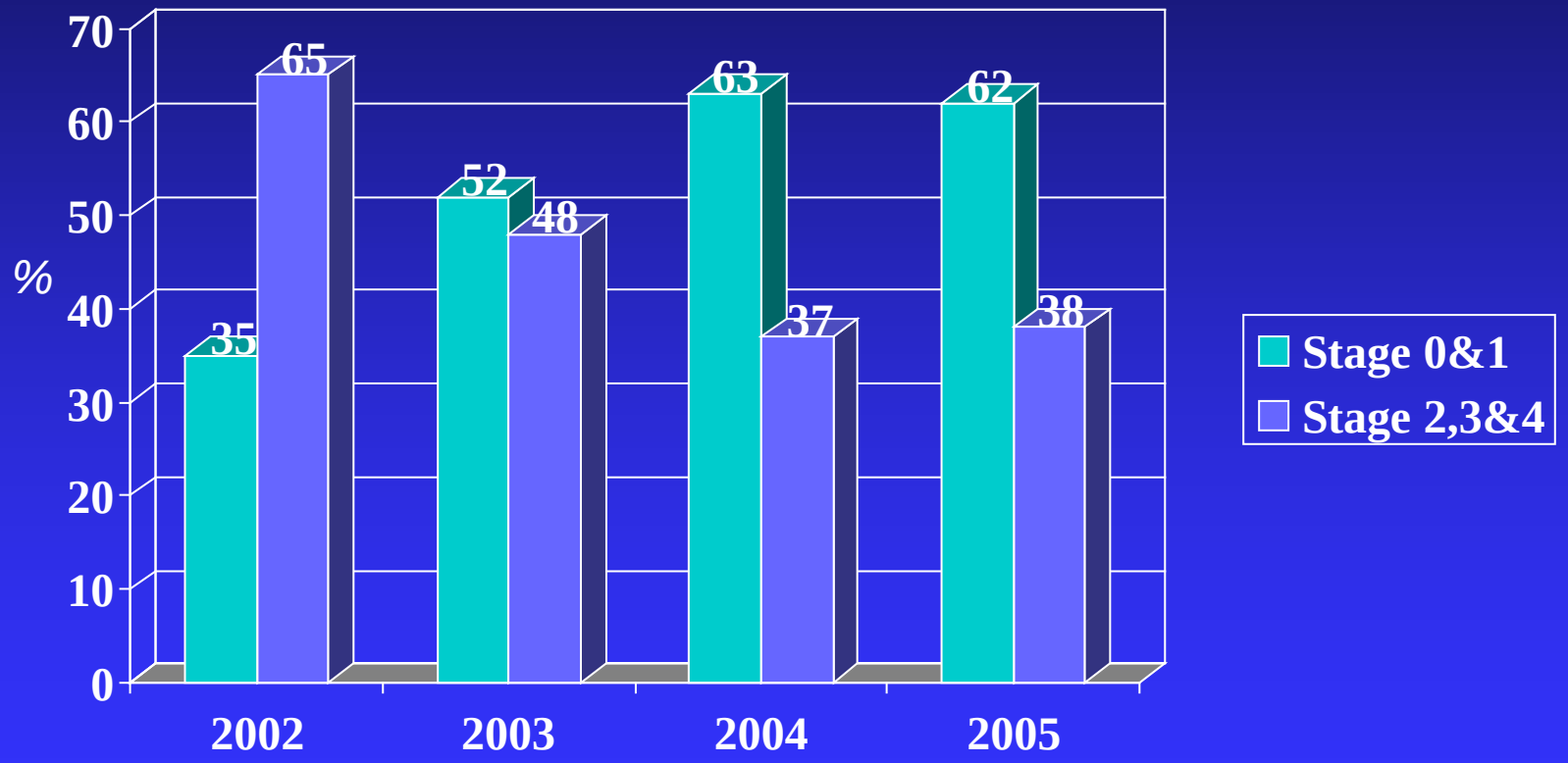
Effect of CRC Screening Program in Colonoscopy Volume, Detected Adenomas, & Revenue

Lincoln Medical Center



Effect of CRC Screening Program in Stage of Detected Cancer

Lincoln Medical Center



Promote routine colonoscopy for outpatients age 50 or older

- Internal Medicine
- Family Medicine
- Gynecology
- Geriatrics
- Smoking cessation
- Mammography
- Diabetes
- Give “Passport to your Health” to patients
- “Physician alert” for patients over 50.
- Places of Worship
- Community Organizations
- Barbershop/ Beauty salons
- Senior Centers
- Libraries
- Query billing system/medical records for patients turning 50
- Employee newsletters
- Insurance forms

Use “Direct Endoscopy Referral System” (Open Access)

- All patients except:
  - Acute GI bleeding
  - Mental handicap or dementia.
  - Previous problems with sedation/ anesthesia.
  - On anticoagulants/ anti-platelets
  - Age 76 or older
  - Co-morbidity with life expectancy less than 5 years
  - Hearth failure, or poorly controlled angina or hypertension
  - Diabetes or severe emphysema (if coordination with Primary Care is limited)

Use “Navigators” to decrease “no-show” and “poor-prep” rates

- Trained “one-on-one” educators
- Use appropriate literacy approach
  - Addresses fears & explains procedure
  - Explains/encourage adherence to bowel prep
  - Encourages adherence to appointment (pre-calls)
  - Identify those needing “financial counseling”.
- Prioritize appointments according to “risk”.
- Are “Follow-up” Managers (surgery/ next colonoscopy)
- Do “Data Tracking” (in Database)
- Evaluate Data for “Benchmarking” and “Quality Assurance”

Implement “Triage”: Screen Higher-Risk First

- **1.** Symptoms or Signs: Rectal Bleeding, Anemia, abnormal Barium enema or CT scan.
- **2.** Inherited Disorder with CRC risk, or IBD
- **3.** Positive FOBT
- **4.** Symptoms without bleeding nor obstruction
- **5.** Family history of colorectal neoplasia
- **6.** Asymptomatic age 50-75 without previous colonoscopy

Use a “social worker” to assist “self-pay” patients

- At Woodhull Medical Center, 20% of “self-pay” were found to qualify for Medicare or Medicaid.
- True “self-pay” should be evaluated by “family-income-scale”, and charged according to a reduced “sliding-fee-scale”.
- Patients should sign a contract to pay in several installments.

Identify patients likely to slow “throughput” and schedule them late in the day.

- History of difficult colonoscopy
- History of pelvic surgery or radiation
- History of diverticular disease.
- Age 76 or older.
- Obese.
- Known to have co-morbidities (except DM which is better to do early in am)
- Non-adherent to scheduled appointment time.

Functions of "Navigator" in Patient Intake
Mount Sinai CRC Screening Program

- MD reviews "open access" cases and appropriate cases are given to Navigator.
- Navigator does the following:
  - 1. Scheduling: interview or phone call.
  - 2. Reminder post-card
  - 3. Two-week reminder call
  - 4. Three-day reminder call

Scheduling interview or phone call.

- Reviews with the patient:
  - Reason for colonoscopy
  - Importance of having a colonoscopy
  - Current medications
  - Explains and gives/mail prep materials
  - Ensures escort
  - Answers all questions
  - Address concerns

Reminder post-card

- Date & Time of Colonoscopy
- Time at which the patient (and escort) should arrive
- Name of Physician who will perform colonoscopy
- Place where the procedure will be done
- Phone number of Navigator, to ask questions or reschedule the colonoscopy.

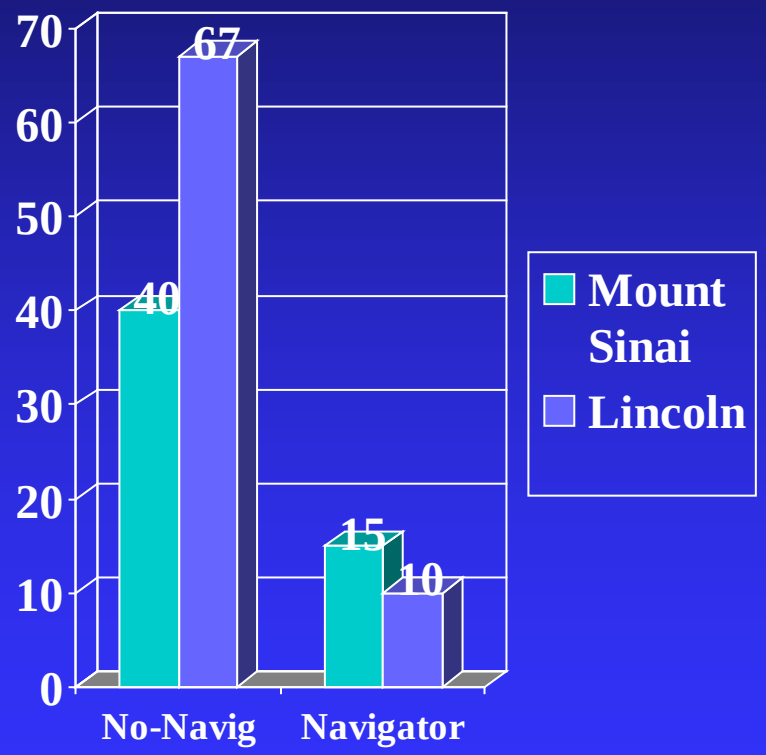
Two-week & Three-day reminder call

- Confirm receipt of prep, and how to perform prep.
- Review importance of colonoscopy and importance of excellent prep.
- Confirm appointment time & location.
- Confirm escort.
- Answer all questions.
- Address concerns.

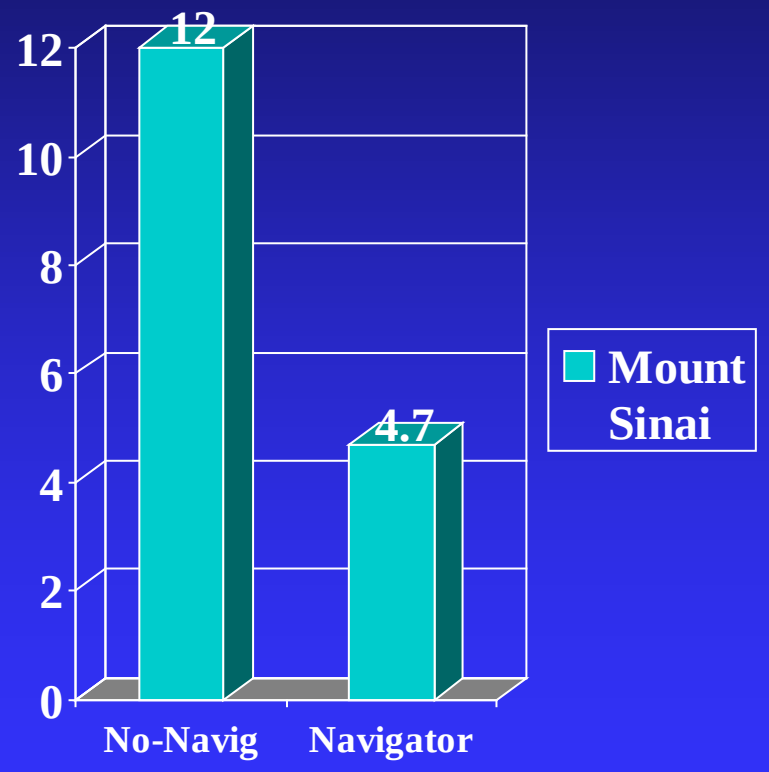
Effect of Navigator

New York City Experience

No-Show Rate



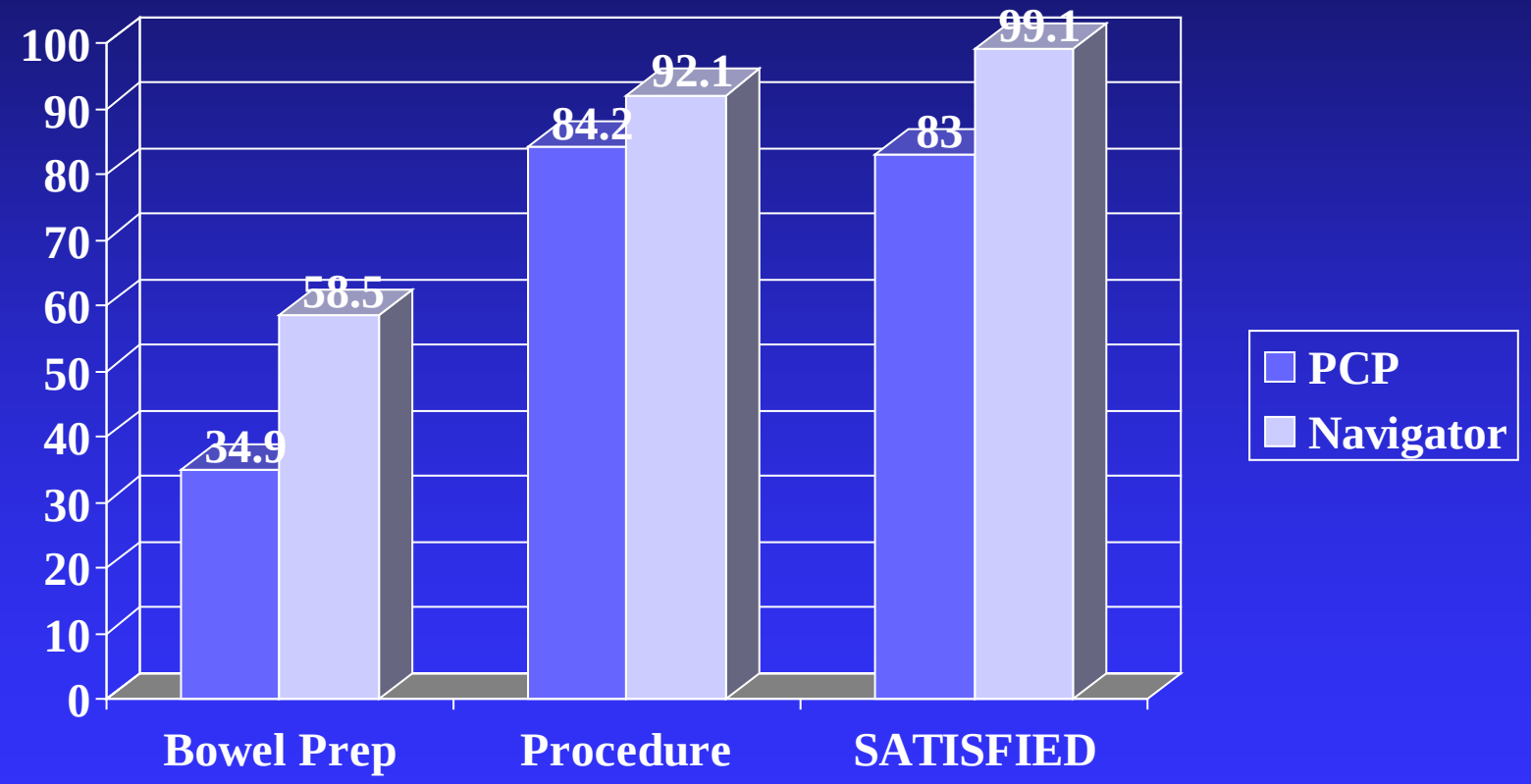
Inadequate/Poor Prep



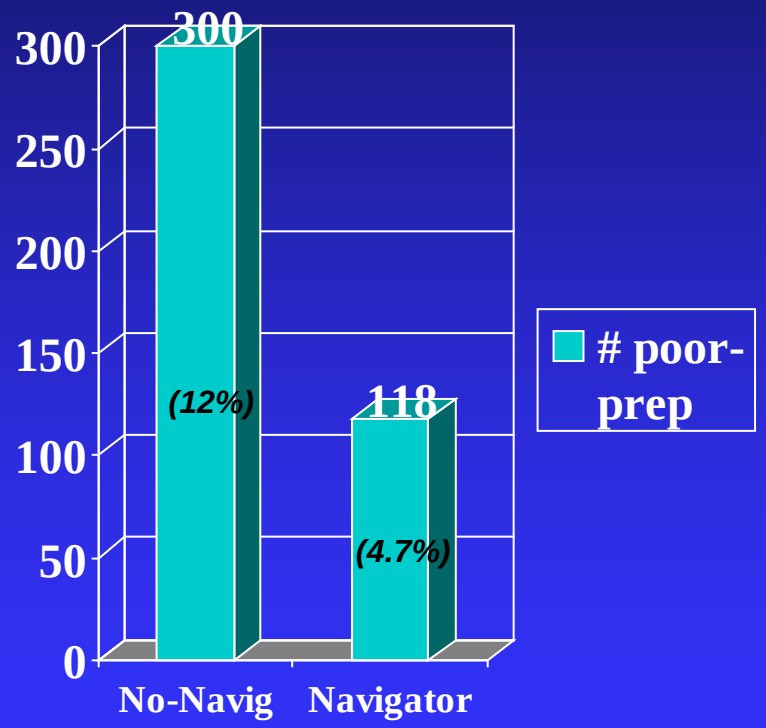
Patient Satisfaction

Understanding Explanations: PCP vs Navigator

(Mount Sinai Hospital – New York)

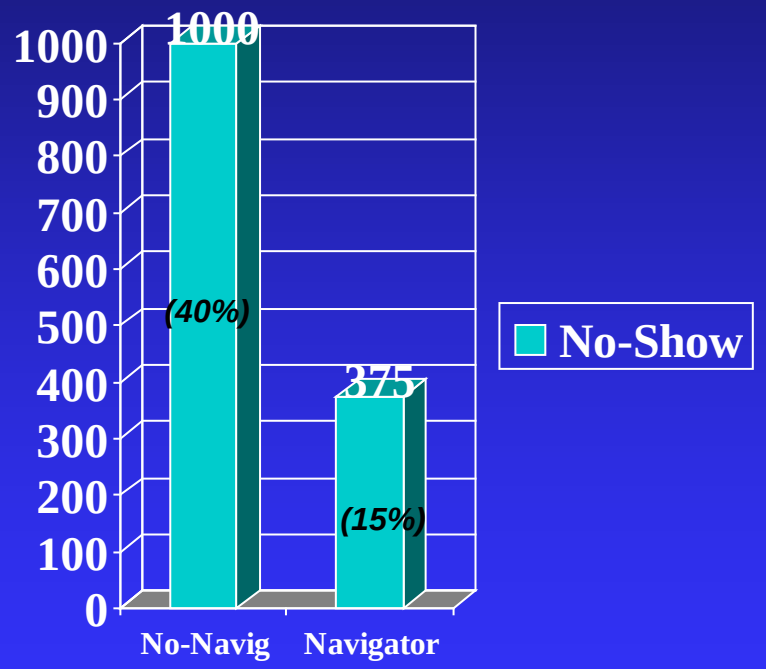


Financial Hospital Implications:
Navigator & Better prep-rates



- Assumes 2500 colon/y
- No change in overhead
- 182 more completed colonoscopies (300-118)
- Facility fee: $ 700/pt
- **Revenue** = 700x182 = **$ 127400**

Financial Hospital Implications:
Navigator & Better no-show rates



- Assumes 2500 colon/y
- No change in overhead
- 625 more completed colonoscopies (1000-375)
- Facility fee: $ 700/pt
- **Revenue** = 700x625 = **$ 437500**

Financial Hospital Implications:
Navigator & Better Efficiency

- Currently ENDO is NOT working at MAX
- No change in overhead
- With increase demand we could accept 15 more colon per week
- Facility fee: $700/pt
- Revenue: 15 pts x 48 wks x 700 = **$ 504000**

- Better prep= **127400**
- Less no-show=**437500**
- Efficiency= **504000**

- **TOTAL = 1068900**

Thank you for your attention.
Questions ?

Differences From Prior Postpolypectomy Guidelines

1. Identify predictors of subsequent advanced adenomas and cancers to stratify patients into lower- and higher-risk groups

2. Risk stratification used to encourage a shift from intense surveillance to surveillance based on risk – free up endoscopic resources for screening, diagnosis, and appropriate surveillance

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Differences From Prior Postpolypectomy Guidelines

3. High-quality baseline colonoscopy is emphasized

4. Completeness of polypectomy at baseline is emphasized – particularly in the setting of piecemeal removal of large sessile polyps

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Differences From Prior Postpolypectomy Guidelines

5. Follow-up surveillance of hyperplastic polyps is discouraged (except in hyperplastic polyposis)

6. The importance of increasing awareness of hyperplastic polyposis is discussed

7. The use of FOBT during surveillance is discouraged at present, but requires further study (low PPV)

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Differences From Prior Postpolypectomy Guidelines

8. Follow-up intervals after removal of 1 or 2 small (< 1 cm) adenomas have been lengthened (5–10 years or average-risk screening options)

9. Evolving technologies such as chromoendoscopy, magnification endoscopy, and CT colonography (virtual colonoscopy) are not yet established as surveillance modalities

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Postpolypectomy Surveillance Recommendations

1. Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies – subsequent colonoscopy should be 10 years.

   Exception is patients with a hyperplastic polyposis syndrome who need to be identified for more intensive follow-up evaluation (increased CRC/adenoma risk)

2. Patients with only 1 or 2 small (< 1 cm) tubular adenomas or serrated adenoma with only low-grade dysplasia should have their next follow-up colonoscopy in 5–10 years.

   Timing should be based on:

   - prior colonoscopy findings,
   - family history,
   - preferences of the patient and
   - judgment of the physician)

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Postpolypectomy Surveillance Recommendations

3. Patients with:
   - 3 to 10 adenomas/serrated adenomas, or
   - any adenoma/serrated adenoma ≥1 cm, or
   - any adenoma with villous features, or
   - high-grade dysplasia

should have their next follow-up colonoscopy in 3 years (providing that piecemeal removal has not been performed and the adenoma(s) are removed completely).

If the follow-up colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Postpolypectomy Surveillance Recommendations

4. Patients who have more than 10 adenomas/serrated adenomas at 1 examination should be examined at a shorter (< 3 y) interval,
    1. Timing established by clinical judgment,
    2. Clinician should consider the possibility of an underlying familial syndrome

Postpolypectomy Surveillance Recommendations

5. Patients with sessile adenomas that are removed piecemeal should be considered for follow-up in 2–6 mo to verify complete removal.

   - Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment;

   - Completeness of removal should be based on both endoscopic and pathologic assessments

6. More intensive surveillance is indicated when the family history may indicate HNPCC

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Additional Surveillance Considerations

1. Recommendations assume that:
   - colonoscopy is complete to the cecum, and
   - bowel preparation is adequate.

   Repeat examination if the bowel preparation is not adequate before planning a long-term surveillance program

2. There is clear evidence that the quality of examinations is highly variable; continuous quality improvement process is critical to the effective application of colonoscopy in colorectal cancer prevention

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Additional Surveillance Considerations

3. A repeat examination is warranted if there is a concern that the polyp was removed incompletely, particularly if it shows high-grade dysplasia

4. Endoscopists should make clear recommendations to primary care physicians about when the next colonoscopy is indicated

Additional Surveillance Considerations

5. Given the evolving nature of guidelines, it is important that physicians and patients should remain in contact so that surveillance recommendations reflect changes in guidelines

6. Pending further investigation, performance of FOBT is discouraged in patients undergoing colonoscopic surveillance (low PPV)

7. Discontinuation of surveillance colonoscopy should be considered in patients with serious comorbidities with less than 10 years of life expectancy, according to the clinician's judgment

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Additional Surveillance Considerations

8. Surveillance guidelines are intended for asymptomatic people; new symptoms may need diagnostic work-up

9. The application of evolving technologies such as chromoendoscopy, magnification endoscopy, narrow band imaging, and computed tomography colonography are not established for postpolypectomy surveillance at this time

Differences Between This Guideline and Previous Guidelines on Postcancer Resection Surveillance Colonoscopy

- In addition to careful perioperative clearing of the colorectum for synchronous lesions, a colonoscopy is recommended 1 year after surgical resection because of high yields of detecting early second, apparently metachronous cancers

- Clinicians can consider periodic examination of the rectum for the purpose of identifying local recurrence after low anterior resection of rectal cancer

Gastroenterology- 2006 (Vol. 130, Issue 6: 1865-1871)

Additional Recommendations Regarding Postcancer Resection Surveillance Colonoscopy

1. Recommendations assume that colonoscopy is:
   - complete to the cecum and that
   - bowel preparation is adequate

2. Continuous quality improvement process is critical

3. Endoscopists should make clear recommendations to primary care physicians about when the next colonoscopy is indicated

4. Performance of fecal occult blood test is discouraged

Gastroenterology- 2006 (Vol. 130, Issue 6: 1865-1871)

Additional Recommendations Regarding Postcancer Resection Surveillance Colonoscopy

5. Discontinuation of surveillance colonoscopy should be considered in persons with advanced age or comorbidities (<10 years life expectancy), according to the clinician's judgment

6. Surveillance guidelines are intended for asymptomatic people

7. Chromoendoscopy (dye-spraying) and magnification endoscopy are not established as essential to screening or surveillance

8. CT colonography (virtual colonoscopy) is not established as a surveillance modality

Gastroenterology- 2006 (Vol. 130, Issue 6: 1865-1871)

Familial Colon Cancer Syndromes

- Hereditary nonpolyposis colorectal cancer (HNPCC)
- Familial adenomatous polyposis (FAP)
- Attenuated familial adenomatous polyposis (AFAP)
- MYH associated adenomatous polyposis (MAP)
- Peutz-Jeghers syndrome
- Familial Juvenile polyposis coli (FJP)

HNPCC

- Muir-Torre syndrome:

  autosomal dominant, sebaceous gland tumors with or without keratoacanthomas, visceral malignancies – a subset of these represent a variant of HNPCC

- Turcot syndrome with glioblastoma:

  HNPCC with CNS tumors (glioblastoma)

HNPCC - Bethesda Guidelines

(For identification of patients with colorectal tumors who should undergo testing for microsatellite instability)

B1 - Individuals with cancer in families that meet the Amsterdam Criteria

B2 - Individuals with 2 HNPCC-related tumors, including synchronous and metachronous colorectal cancer or associated extracolonic cancer (endometrium, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional-cell carcinoma of the renal pelvis or ureter)

B3 - Individuals with colorectal cancer and a first-degree relative with colorectal cancer or HNPCC-related extracolonic cancer or a colorectal adenoma; one of the cancers diagnosed at age <50 years, and the adenoma diagnosed <40

B4 - Individuals with colorectal cancer or endometrial cancer diagnosed at age <50 years

B5 - Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid, cribriform) on histopathology diagnosed at age <50 years (solid or cribriform), defined as poorly differentiated for undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces

B6 - Individuals with signet-ring-cell type colorectal cancer diagnosed at age <50 years (composed of >50% signet-ring cells)

B7 - Individuals with adenomas diagnosed at age <40 years

Screening and Surveillance in HNPCC

- Definite or potential gene carriers are screened by colonoscopy every 2 yrs beginning at age 20-25 yrs until age 40 yrs and then annually
- Patients who develop advanced adenoma and proven gene carriers can be offered prophylactic subtotal colectomy followed by annual proctoscopy and polypectomy

Gastroenterology- 2006 (Vol. 130, Issue 6: 1872-1885)

Other Screening/Surveillance in HNPCC (Published Expert Opinion)

- Annual screening for endometrial and ovarian cancer at age 25-30 yrs
- Annual UA with cytologic exam at 25 for increased risk of renal/urinary tract cancer
- Discussion of prophylactic hysterectomy and BSO at age 35/end of child bearing
- Annual skin survey
- Periodic upper endoscopy (possibly starting age 30?)

FAP

- Lifetime risk of colon cancer is 100%
- Average age of adenoma appearance = 16 yrs
- Average age of colon cancer = 39 yrs

FAP

- Gardner's syndrome:

  FAP (same APC gene mutation) with prominent extraintestinal manifestations – desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas (especially mandible), supernumerary teeth, gastric polyps and juvenile nasopharyngeal angiofibromas

- Turcot syndrome with medulloblastoma:

  FAP variant associated with medulloblastoma

FAP – Screening and Surveillance

- Gene carriers or at-risk family members – flexible sigmoidoscopy every 12 months starting with age 10-12

  (some pediatric gastroenterologist are offering colonoscopies)

- Discontinue annual colon examination at age 40 if negative till then

FAP – ASGE guidelines for screening and surveillance of upper GI tract

- Patients with FAP should undergo upper endoscopy with both end-viewing and side-viewing instruments
- The optimal timing of initial upper endoscopy is unknown – could be performed around the time the patient is considered for colectomy or early in the third decade of life
- If no adenomas are detected, another exam should be performed in five years because adenomatous change may occur later in the course of the disease

FAP – ASGE guidelines for screening and surveillance of upper GI tract

- For patients with duodenal and periampullary adenomas – surveillance endoscopy and biopsy should be performed at intervals based on stage of disease
- Endoscopic treatment of papillary adenomas may be appropriate in selected patients
- If excision is complete, one approach is for follow-up endoscopy and multiple biopsies every six months for a minimum of two years, with endoscopy thereafter at three-year intervals

FAP – ASGE guidelines for screening and surveillance of upper GI tract

- Duodenal polyps should be biopsied or sampled at the time of initial discovery and on each subsequent examination to determine the stage of duodenal polyposis
- The frequency of exams and referral for prophylactic surgery are determined on the basis of duodenal polyp stage

FAP – ASGE guidelines for screening and surveillance of upper GI tract

- Gastric polyps – biopsy to confirm that they are fundic gland polyps and to assess for dysplasia.
- Antral polyps - usually adenomas, should be resected.

Attenuated FAP – Screening and Surveillance

- Annual colonoscopy in the late teens or early 20s – depending age of polyp expression in family
- Continue surveillance longer than FAP
- Upper endoscopy screening and surveillance like FAP

MAP (MYH associated polyposis) – Extracolonic manifestations

- No current guidelines for screening/surveillance
- Some experts recommend C-scope starting at 18 yrs
- Other recommend both upper and lower endoscopy starting at 25-30 yrs

Peutz-Jeghers Syndrome – Surveillance

- From birth to age 12:

  Male patients:

  H & P with attention to the testicles.

  Routine blood tests annually (optional - ultrasound of the testicles every two years until age 12).

  Female patients:

  H & P with routine blood tests annually

- At age 8:

  Males and females:

  Upper endoscopy and small bowel series; if positive, continue every two to three years

Clinical Gastroenterology and Hepatology 2006; 4:408

Peutz-Jeghers Syndrome – Surveillance

- From age 18:

  Male patients: colonoscopy, upper endoscopy, and small bowel series every two to three years.

  Female patients: Colonoscopy, upper endoscopy, and small bowel series every two to three years; breast self-exam monthly.

  (Future alternatives to small bowel series: wireless capsule endoscopy; push-enteroscopy or double-balloon enteroscopy - therapeutic intervention, but invasive)

- From age 21:

  Female patients: pelvic examination with a Papanicolaou smear annually

Clinical Gastroenterology and Hepatology 2006; 4:408

Peutz-Jeghers Syndrome – Surveillance

- From age 25:

  Male patients:

  EUS of the pancreas every one to two years (CT scan and/or CA19-9 offered as options):

  Female patients:

  EUS of the pancreas every one to two years (CT scan and/or CA 19-9 offered as options)

  clinical breast exam semiannually;

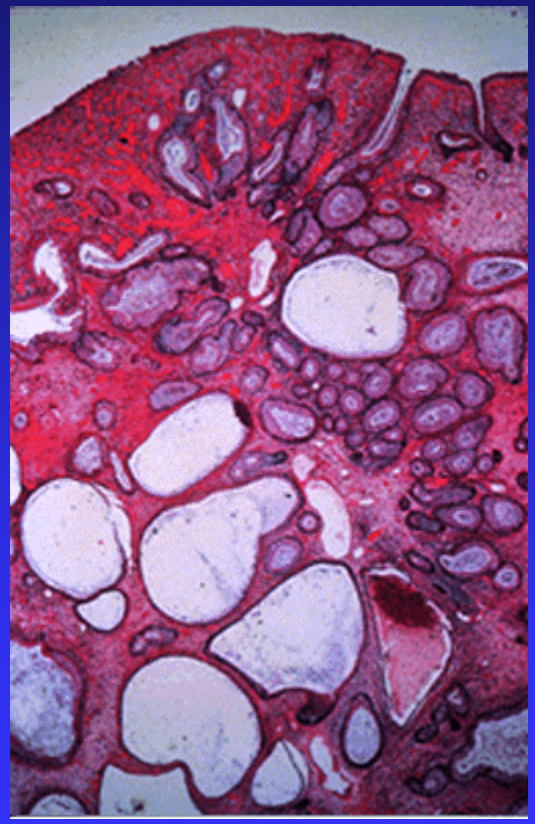
  mammography annually (alternative – MRI);

  transvaginal ultrasound and serum CA-125 annually.

  Mammography might begin earlier on the basis of earliest age of onset in the family

Clinical Gastroenterology and Hepatology 2006; 4:408

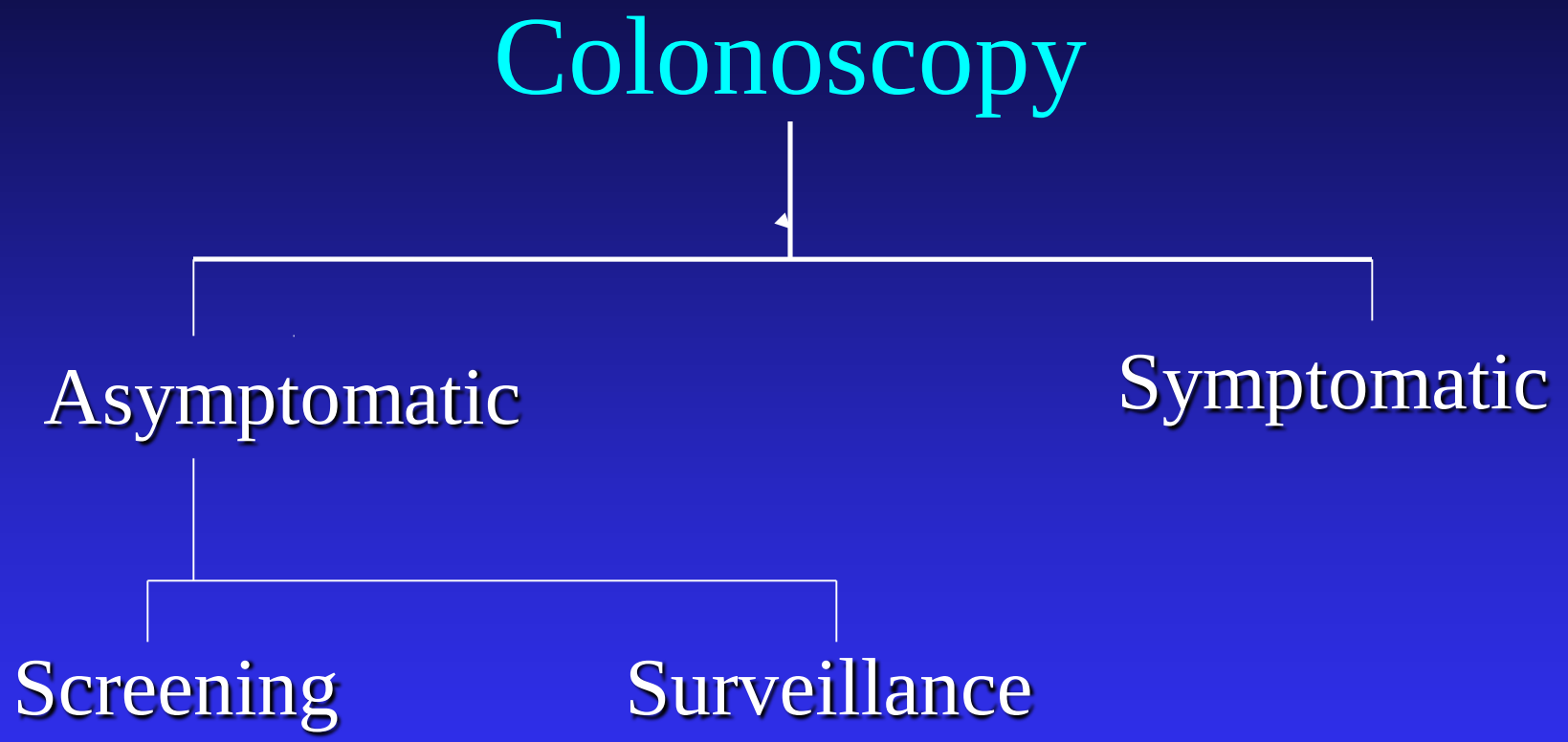
Familial Juvenile Polyposis



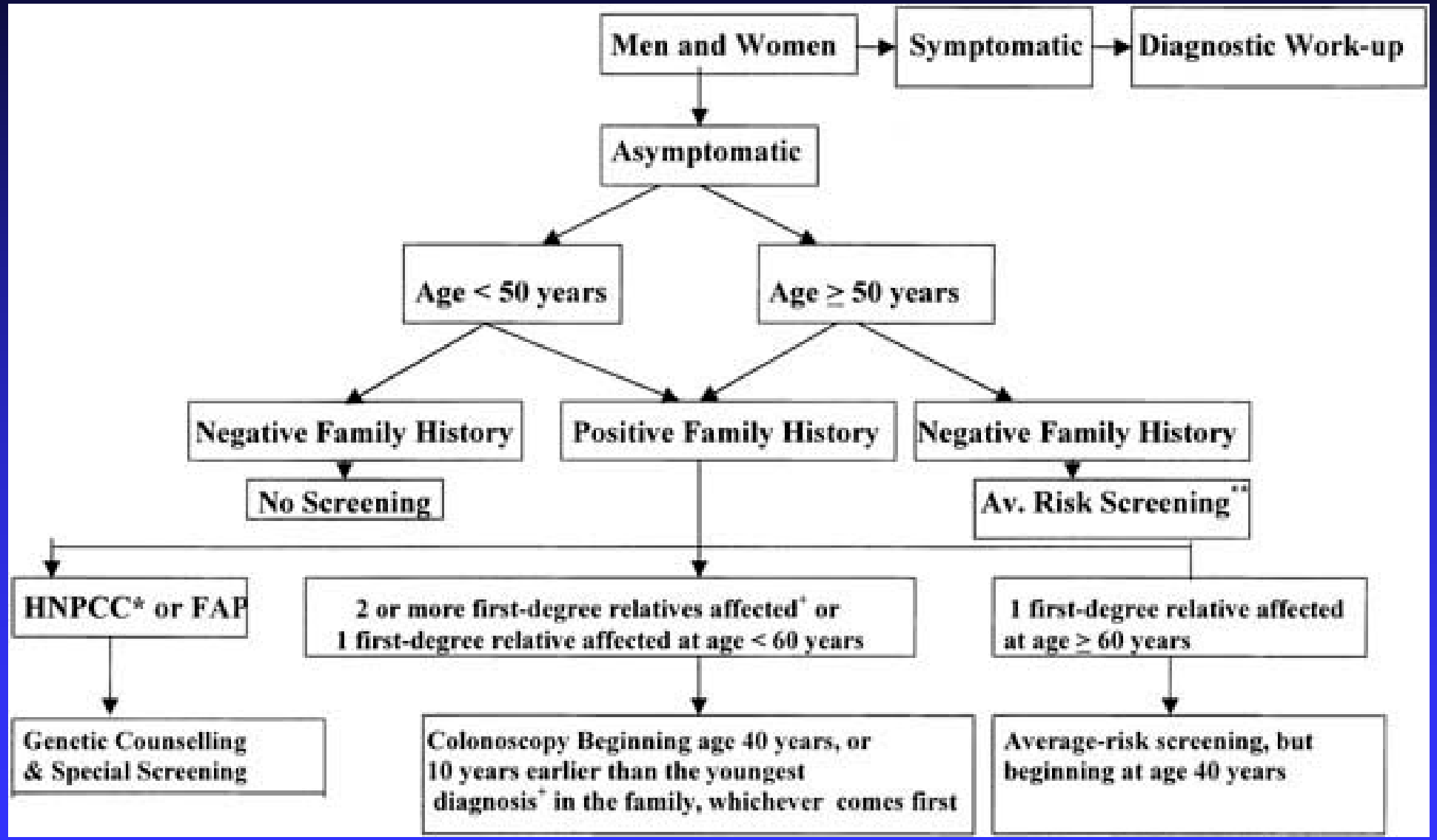
Familial Juvenile Polyposis – Surveillance and Screening

- At risk individuals – colonoscopy every 1-2 yrs beginning age 15-18
- Upper endoscopy /enteroscopy or UGI with SBFT every 1-2 yrs beginning age 25

Gut 2002; 51 Suppl 5: V21


Colonoscopy
Asymptomatic
Symptomatic
Screening
Surveillance

Screening algorithm



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Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Revised Amsterdam Criteria
by the International Collaborative Group on HNPCC[†]

There should be at least three relatives with an HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)

One should be a first degree relative of the other two

At least two successive generations should be affected

At least 1 should be diagnosed before age 50

Familial adenomatous polyposis should be excluded in the colorectal cancer case(s) if any

Tumors should be verified by pathological examination

[†]Adapted from Vasen, HF, Watson, P, Mecklin, JP, et al. Gastroenterology 1999; 116:1453.

Syndrome of Hyperplastic Polyposis

- Increased risk for colorectal cancer
- Magnitude of increased risk not yet determined
- Optimal management of hyperplastic polyposis has not yet been defined and requires further study

Thank you for your attention.
Questions ?