Colorectal Cancer (CRC) Screening & Surveillance

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CRC in USA

- Lifetime-Risk of CRC is 6%
- Mortality:
  - 56000 per year
  - 10% of cancer deaths
  - 2.3% of all deaths
  - Second cancer killer after Lung Cancer
  - 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.
- 20% of colon adenomas become cancerous
- Half of colon Cancer patients die from CRC

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 40.**
  - Personal History of colon Adenoma or CRC
  - Illness that predisposes to CRC (IBD)
  - Family History of colon Adenoma 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.**

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)

Screening Tools for CRC

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 in 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
  - 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 >/= 10 mm, OR
- Sessile Serrated Polyp 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)

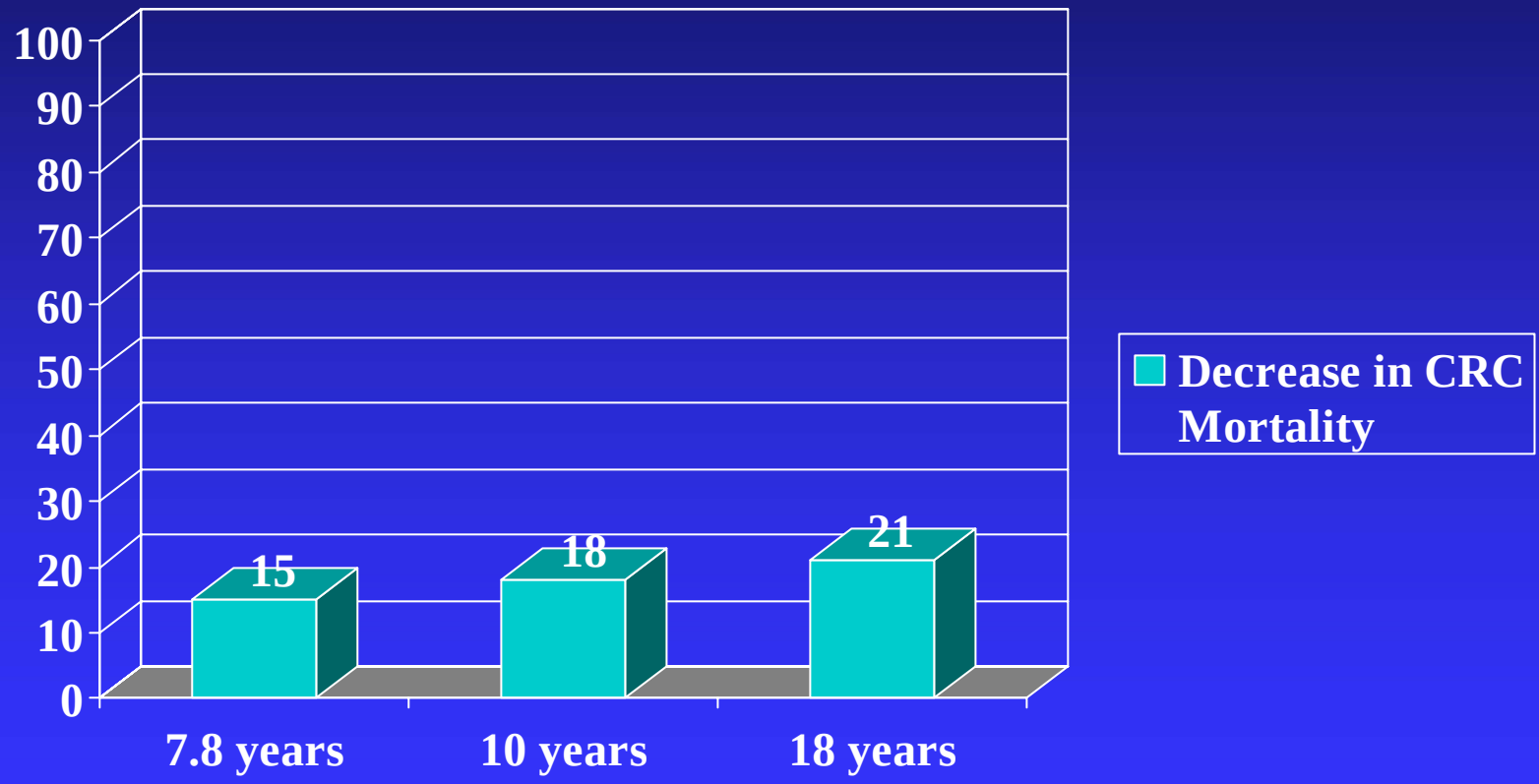
- HP < 10 mm are benign an non neoplastic.
- HP are 50% of polyps 1-5 mm, 27.9% of polyps 6-9 mm, and 13.7% of polyps > 10 mm.
- Neither proximal nor distal HP associated with adenomas are indicative of increased risk of adenomas at 3 y after colonoscopy.
- If the only lesions at colonoscopy are distal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

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.
  - **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.

Testing Alternatives

CA Cancer J Clin 2008

- **Double-Contrast Barium Enema every 5 years.**
  - Case-controlled study:
    - 33% reduction CRC deaths
  - ACBE compared with colonoscopy:
    - detects 53% of 6-10 mm adenomas, and
    - 48% of adenomas > 1 cm,
  - In community practice: DCBE detects 85% of colon Ca (vs colonoscopy 95%).

Testing Alternatives

CA Cancer J Clin 2008

- **CT Colography 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%

Testing Alternatives

CA Cancer J Clin 2008

- **Stool DNA Analyses; interval undefined**
  - Rationale:
    - Detects molecular changes associated to advanced CRC (and other Ca).
    - sDNA analyses was superior to low-sensitivity FOBT (Hemoccult-II) for detection of:
      - CRC: 52% vs 13%, and for
      - All cancer & HGD: 40.8% vs 14.1%
      - Advanced adenomas.

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
  - 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.

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)**

Stratification of CRC Screening by Risk Factors

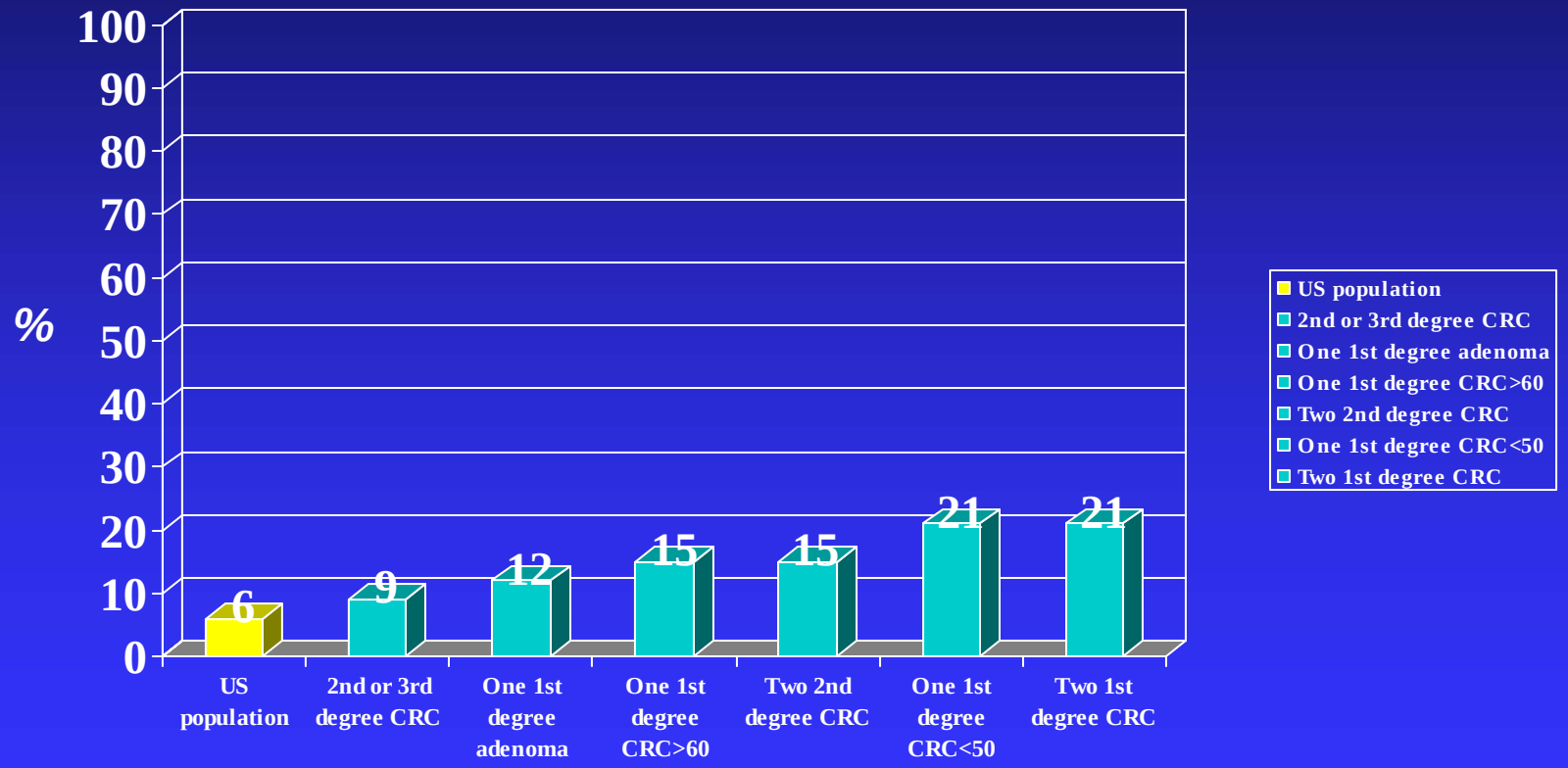
Average Risk for CRC

- "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.

Increased-Risk for CRC

Familial Risk

Familial Risk
Lifetime Risk of CRC



Effect of Family History on Onset & Frequency of Screening Colonoscopy

Category	Start age (the lesser)	Interval
One 2nd degree, or any number 3rd degree with CRC	50	10 years
1st degree with CRC =/> age 60	40	10 years
1st degree with adenoma =/> age 60	40	10 years
Two 2nd degree with CRC	40	10 years
1st degree with adenoma or CRC < age 60	40, or [10 y before "index"]	5 years
=/> two 1st degree with CRC	40, or [10 y before "index"]	5 years

High-Risk for CRC

Inflammatory Bowel Disease

Inherited Colorectal Cancer Disorders

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

- Increase Risk:
  - disease duration,
  - more extensive disease (above sigmoides),
  - primary sclerosing cholangitis (4X), and
  - family hx of sporadic CRC (1st 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 increase 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

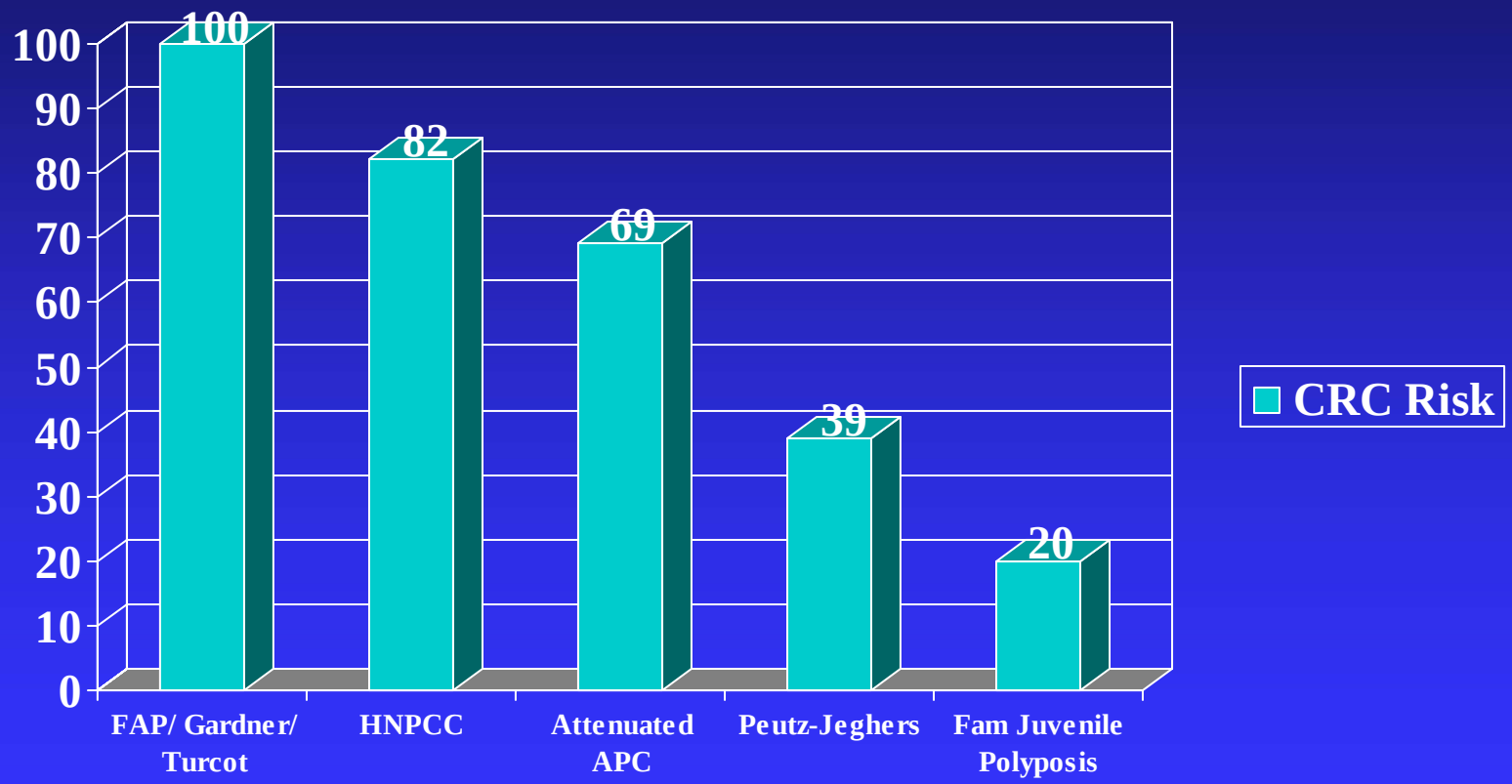
Management of Raised Dysplasia in IBD

- 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 Disorders
Lifetime Risk of CRC



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 > 9 mm adenoma
  - Adenoma in < age 40
  - Adenoma or CRC in person with FH suspicious for HNPCC
- How:
  - Biopsy target lesion (polyp or cancer) and Normal Tissue.
  - IHC (Immuno Hystochem)

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

Juvenile Polyposis Syndrome (JPS)

- Autosomal dominant Hamartomatous Polyposis.
- Incidence < 1/100,000
- Gene (Chromosome18): mutation in SMAD4, or BMPR1.
  - Cytoplasmic mediator in TGF-β signalling.
  - Found in only 40% of JPS.
- May have Hereditary Hemorrhagic Telangiectasia, or congenital defects
- **Diagnosis:**
  - **at least 3 juvenile polyps in the colon,**
  - **multiple JP in the GI tract, or**
  - **any number of JP with family history of JPS**

Juvenile Polyposis Syndrome

- Risk of colon CA – may be up to 39%.
- Increased risk of Gastric, pancreas & small bowel cancer in 21%.
- Strong association with Hereditary Hemorrhagic Telangiectasia.
- Genetic Counseling is recommended.
- CRC Screening: Colonoscopy q 2-3 y beginning with symptoms, or in late teens.
- **Screening for extracolonic tumors is recommended (stomach & small bowel).**

Juvenile Polyposis Syndrome Screening for Extracolonic Tumors

- Gastric & SB polyps and Ca:
  - EGD q 1-3 y +
  - SB series every 1-3 years (depending on polyp burden), starting at age 25
- HHT:
  - Evaluation for clinical evidence of Hereditary Hemorrhagic Telangiectasia (epistaxis, telangiectasia, visceral lesions, family history) which will prompt evaluation for occult AVMs.

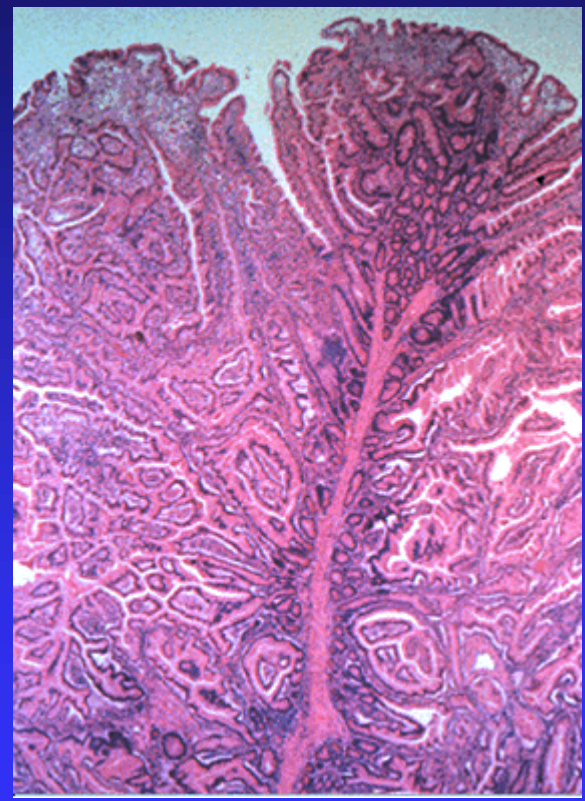
Peutz-Jeghers Syndrome

- Autosomal dominant
- Germ line mutation of a gene on chromosome 19
- Gene encodes a serine threonine kinase
- **Pigmented spots on lips and buccal mucosa**
- **Multiple gastrointestinal hamartomatous polyps** (small bowel: 65-95%; colon: 30-60%; stomach: 25-50%)
- Diagnosis with 2 or more of:
  - 2 or more PJ polyps in small bowel
  - 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.**
- **CRC Screening: Colonoscopy q 2-3 y beginning with symptoms, or in late teens (whichever is first)**

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	< 1%

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 10:
  - a) Males:
    - EGD q 2-3 y
    - SB series or abdominal CT with oral contrast 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+
    - SB series or abdominal CT with oral contrast 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.

MutYH (MYH) Associated Polyposis

- Autosomal recessive
- Biallelic mutations in MYH gene
- 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.**

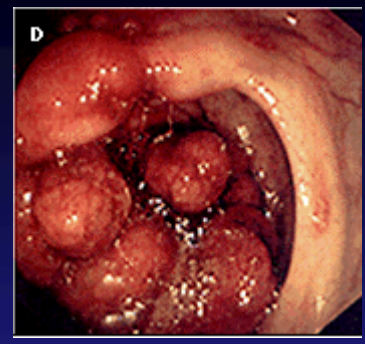
MAP (MYH associated polyposis) – Extracolonic manifestations

- 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.

HNPCC



- Autosomal dominant, 80% penetrance
- Accounts for 1% - 5% of all CRC cases
- Caused by germ-line mutation in 1 of 6 mismatch repair genes [hMSH2 and/or hMLH1 (in > 80%), hMSH6 (in 10%), hPMS1, hPMS2, and hMLH3 (all rare)]
- Mean age for CRC development is 44 with some patients presenting in their 20s
- Predominantly right colon involvement
- Tumors show microsatellite instability (MSI)
- Genetic Counseling is recommended.
- CRC Screening: Colonoscopy q 1-2 y beginning at 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.

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.

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.**

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.

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.

Familial Adenomatous Polyposis (FAP)

- Autosomal dominant
- Mutation in “adenomatous polyposis coli” gene (APC) in chromosome 5.
- APC – is a tumor suppressor gene
- 1/10,000 to 1/30,000 liver births
- 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

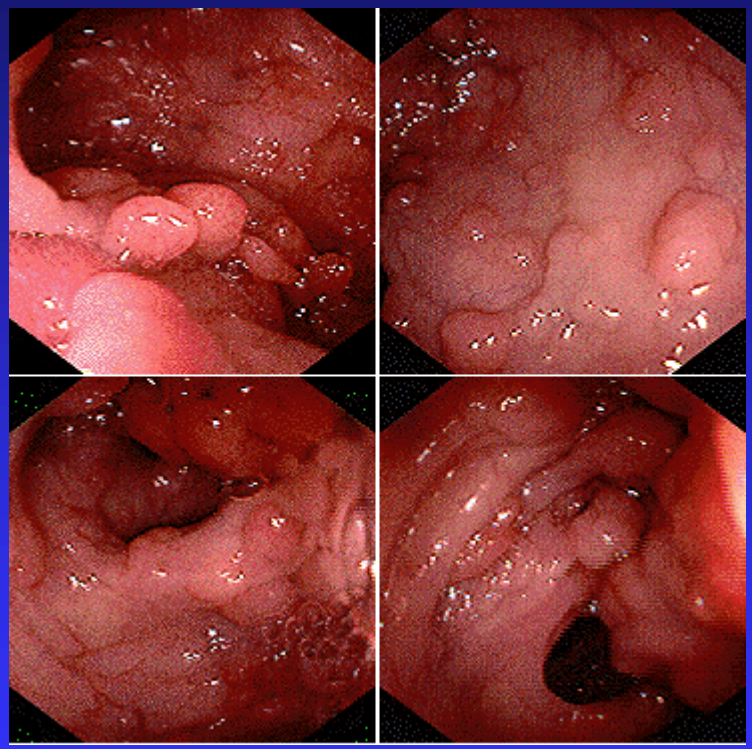
Familial Adenomatous Polyposis (FAP)

- **Diagnosis – > 100 adenomatous colorectal polyps**
- **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 ?

FAP and AFAP
Screening for Extracolonic Tumors

Modified Spigelman's Score and Classification†

	Score		
Factor	**1 Point**	**2 Points**	**3 Points**
Number of polyps	1-4	5-20	>20
Polyp size, mm	1-4	5-10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	--	High grade

Note: Classification: no polyp, stage 0; 1 to 4 points, stage I; 5 to 6 points, stage II; 7 to 8 points, stage III; 9 to 12 points, stage IV.

†Reproduced with permission from: Saurin, J, Gutknecht, C, Napoleon, B, et al. Surveillance of duodenal adenomas in familial adenomatous polyposis reveals high cumulative risk of advanced disease. J Clin Oncol 2004; 22:493. Copyright ©2004 American Society of Clinical Oncology (ASCO).

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)

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) patient refuses frequent colonoscopies, or
  - c) 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.

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.
  - Breast and endometrial cancer screening.
  - Colonoscopy at age 35, then by findings.

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.

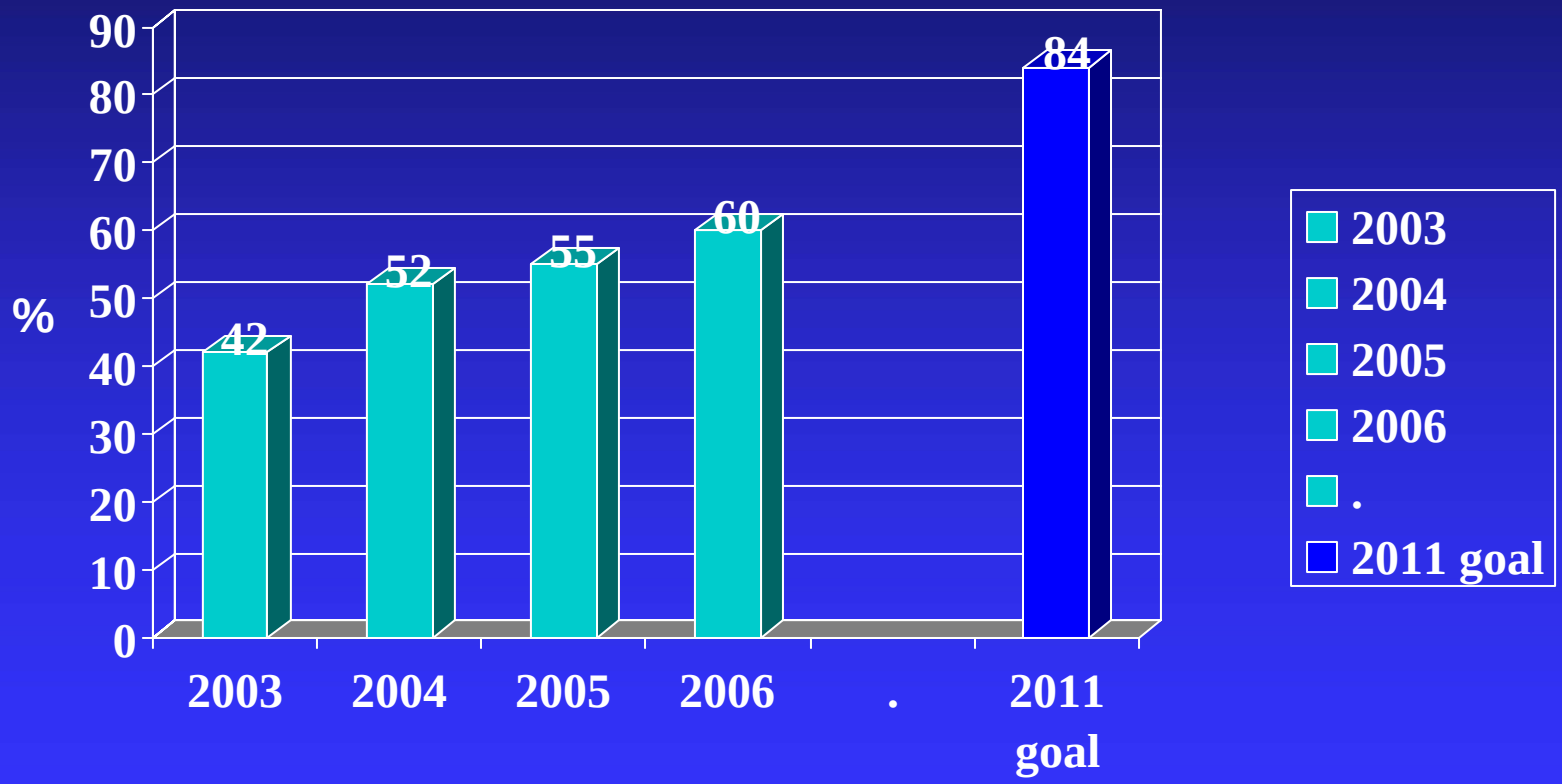
Increasing Colonoscopy Screening

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

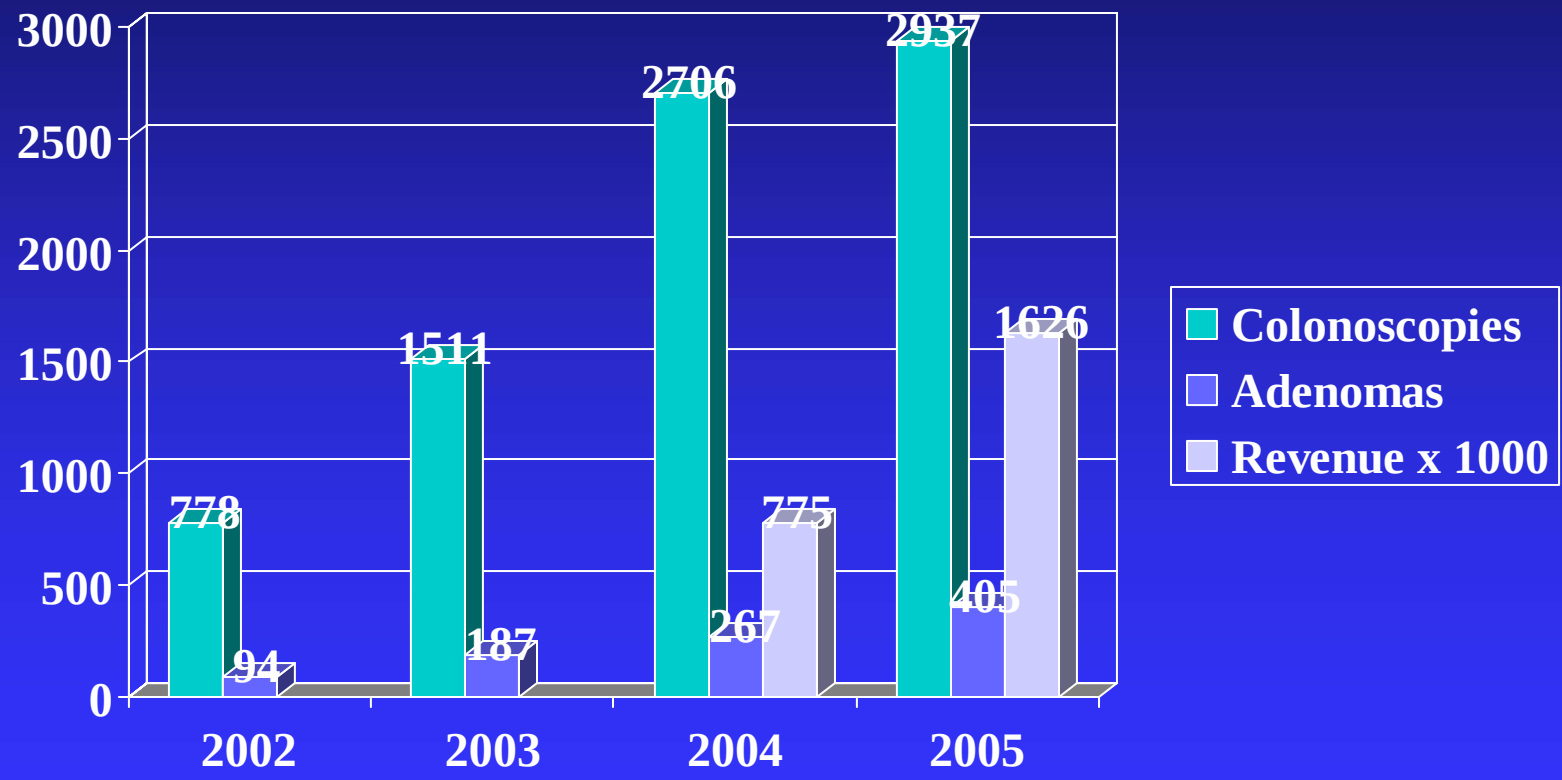
New York City Community Health Survey



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

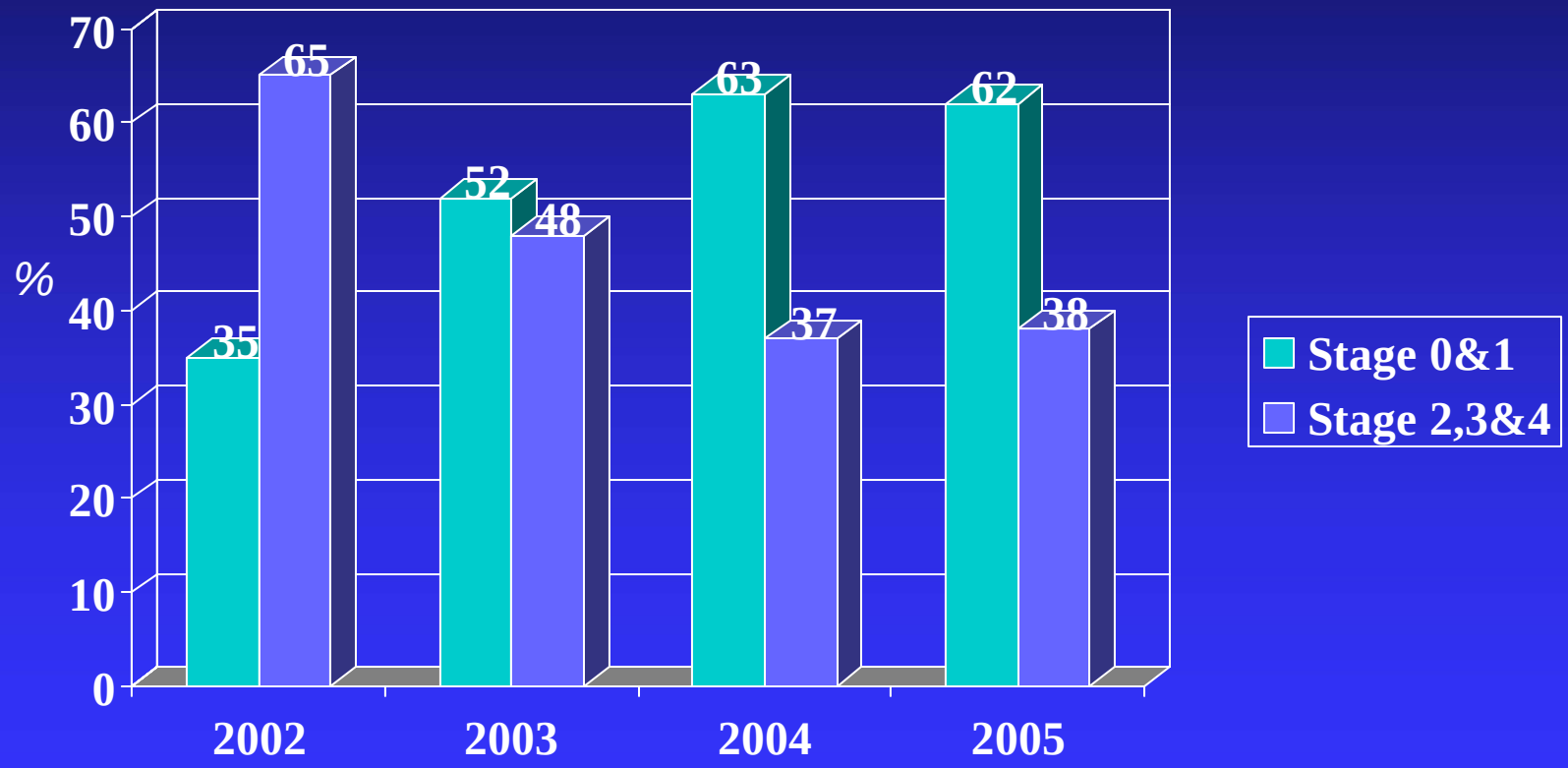
Effect of CRC Screening Program in Colonoscopy Volume, Detected Adenomas, & Revenue

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.

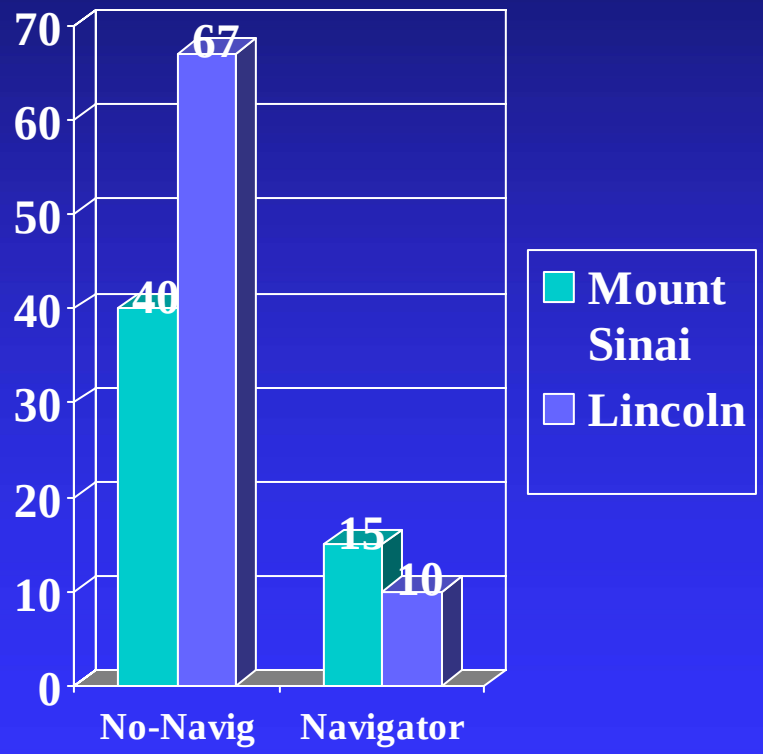
Two-week & Three-day reminder call

- 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.

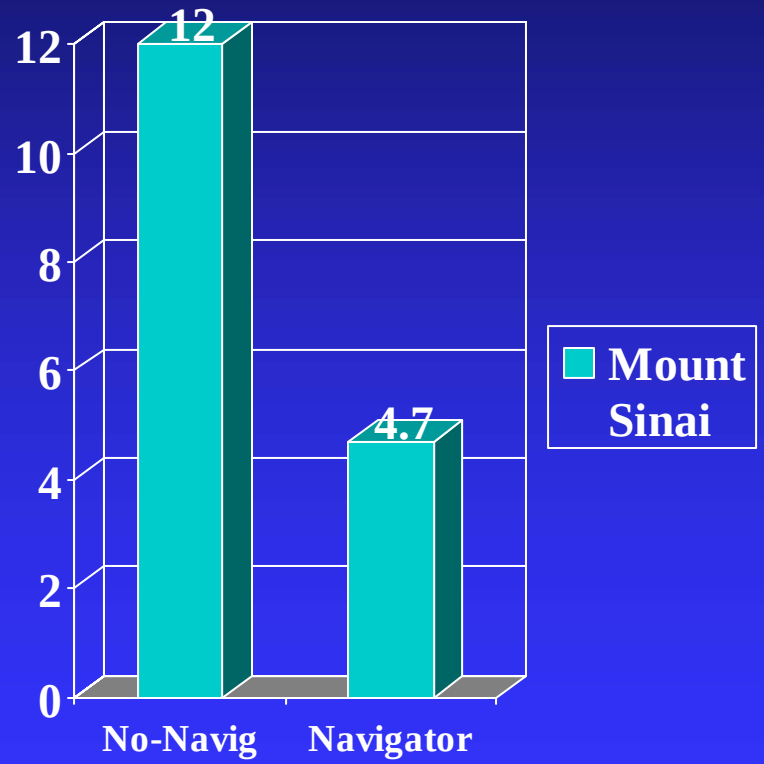
Effect of Navigator

New York City Experience

No-Show Rate



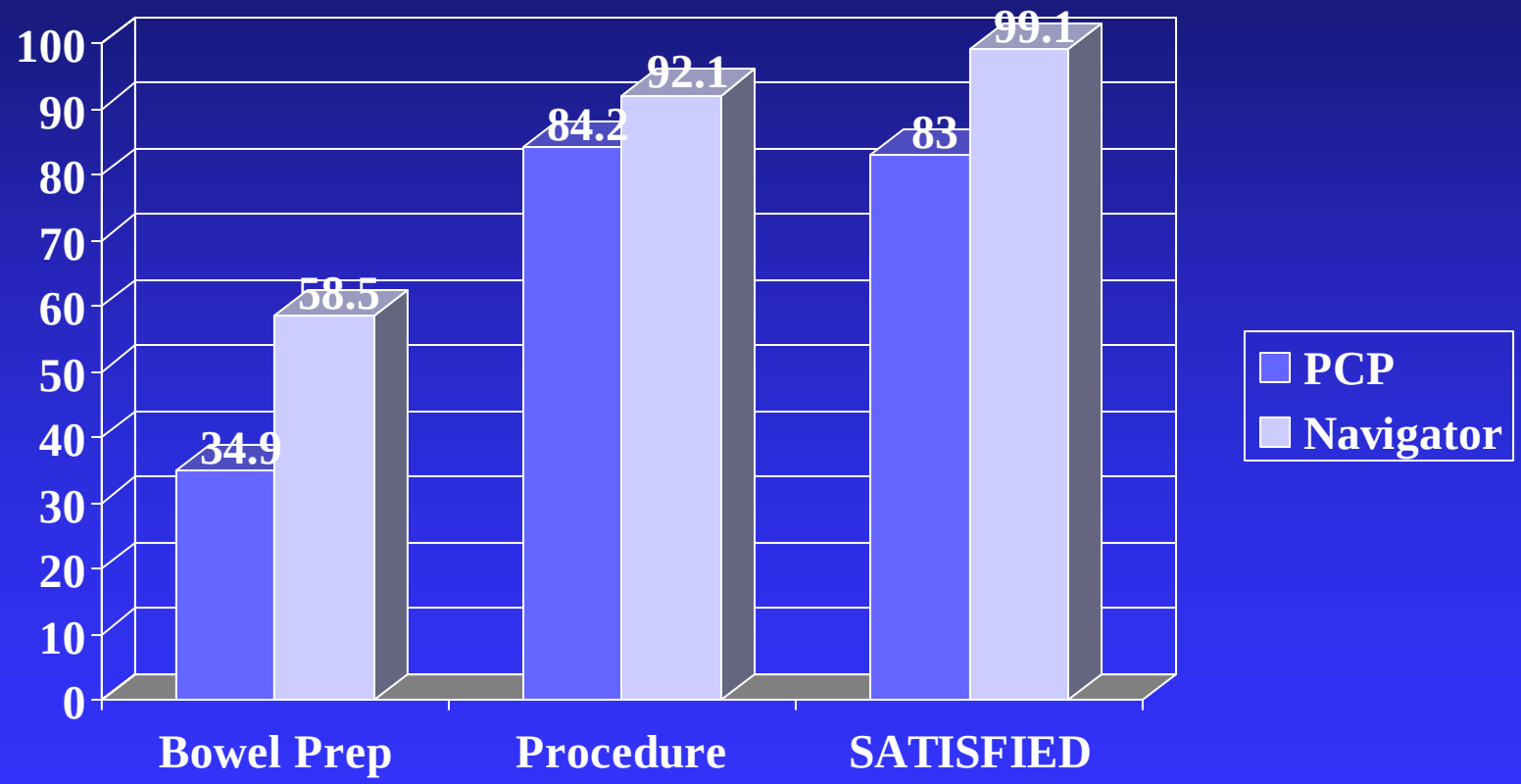
Inadequate/Poor Prep



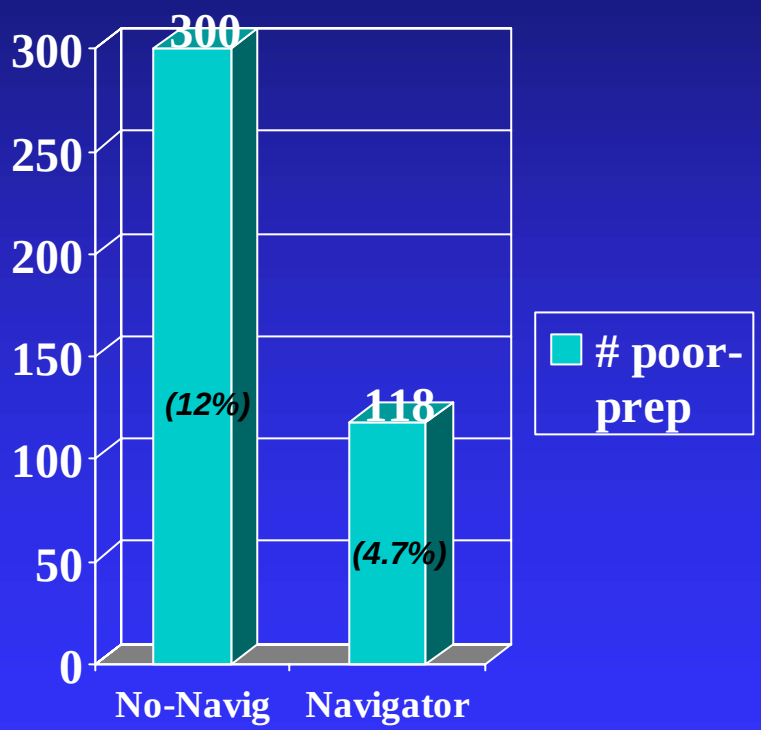
Patient Satisfaction

Understanding Explanations: PCP vs Navigator

(Mount Sinai Hospital – New York)

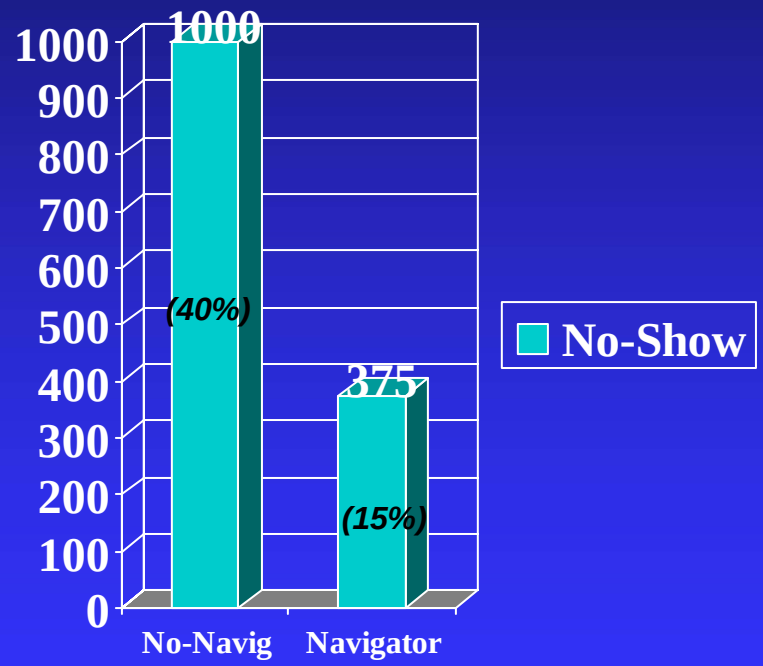


Financial Hospital Implications: **Navigator & Better prep-rates**



- 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**

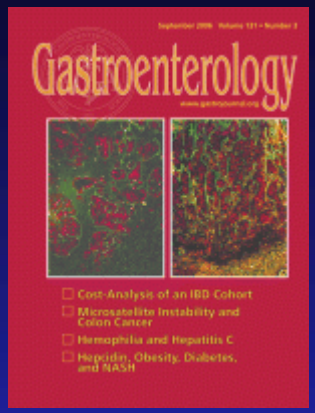
Financial Hospital Implications: **Navigator & Better Efficiency**

- 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**

Colonoscopy Surveillance After Polypectomy, and After Cancer Resection



Gastroenterology- 2012;143:844-857

Guidelines for Colonoscopy Surveillance After Screening and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society

Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR

Surveillance

Surveillance is the examinations that are performed in a patient with known previous disease in an attempt to modify and address future risk

Why new guidelines?

- Large number of patients with adenomas identified
- Surveillance is a huge burden on medical resources
- Need for increased efficiency of surveillance colonoscopy
- Decrease cost, risk and overuse of resources
- **The first screening colonoscopy at age 50 is the one with the most-impact in CRC mortality; excessive "surveillance" affects our ability to offer 1st screening colonoscopy to others.**

Guideline endorsed by:

- Colorectal Cancer Advisory Committee of the American Cancer Society
- American College of Gastroenterology
- American Gastroenterological Association
- American Society for Gastrointestinal Endoscopy

Literature reviewed

- Colonoscopy studies addressing relationship between baseline findings and detection of advanced adenoma during follow up
- Sigmoidoscopy studies with large cohorts and follow-up periods longer than 10 yrs addressing the relationship between baseline findings and detection of advanced adenomas at follow up
- 15 studies were identified

Advanced Adenoma (AA)

- Sized 1.0 cm or larger OR
- Any villous component (nontubular) OR
- High grade dysplasia OR
- Invasive cancer
- **Advanced Adenoma is a surrogate biological-indicator of cancer risk**

Predictors of Subsequent Advanced Adenomas (AA)

- Multiplicity
- Size
- Histology
- Location
- Other risk factors – age, sex, history of polyps, family history of CRC

Multiplicity

- **Increased number of adenomas at baseline has been shown to predict subsequent detection of advanced adenoma (AA)**
  - National Polyp Study (RCT)
  - European fiber and calcium study (RCT)
  - Wheat bran study (Martinez et al) (RCT)
  - Atkin et al (observational cohort)
  - Noshirwani et al (observational cohort)

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

Size

- **Larger adenoma size was related to increased risk for subsequent AA or CRC**
  - Wheat bran study (RCT): size larger than 1 cm predicted metachronous advanced adenomas
  - 4 other RCT did not find size to an independent predictor
  - 7 out of 8 observational cohort studies showed size predicted future AA or CRC

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

Histology

- Overall, presence of villous component and/or high grade dysplasia correlated with increased risk of AA or CRC
  - None of the RCT showed histologic type of adenoma at baseline to be a significant predictor of advanced neoplasia, but
  - Several of the observational cohort studies showed that advanced histology conferred increased risk of AA in follow-up.

IMPORTANT HISTOLOGY CONCEPT

Serrated Adenoma

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

IMPORTANT HISTOLOGY 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.
- **For Surveillance Programs, "Serrated Adenomas" should be treated as regular adenomas.**

Location

- Proximal adenoma found at baseline was associated with an increased risk for subsequent Advanced Adenoma
  - Seen in 2 RCT and 1 observational cohort studies

Other risk factors

- Age
  - 2 RCT showed increased risk for subsequent neoplasia with increased age
- Sex
  - 2 RCT reported an increased risk for men for advanced neoplasia
- History of polyps
  - polyps present before “baseline adenoma” was found are associated with increased risk of more AA (2RCT)
- Family history of CRC
  - in relative >/= 60, increases 4.8 fold the risk of AA in subsequent colonoscopy.
  - increased risk for CRC (2.4 fold with 1 relative; 4.2 fold if > 1) & AA.

FOBT Testing in Post-Polypectomy Patients

- National Polyp Study: 77% of colonoscopies performed to evaluate (+)FOBT detected no AA nor CRC (PPV = 23%)
- Bampton et al: in a high risk cohort, PPV of immunochemical FOBT was only 27%.
- Follow-up colonoscopy intervals based in "risk stratification" are conservative and shortening the interval due to a (+) FOBT is unlikely to improve over the current 76-90% CRC incidence reduction.
- **In patients in a "surveillance colonoscopy program", the use of FOBT is currently discouraged.**

High-quality Baseline Colonoscopy

- **Should be satisfied before starting Screening or Surveillance Program.**
- **Critical for effectively reducing colon cancer risk.**
  - **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 used (repeat exam if needed)**

Surveillance Intervals after Polypectomy

Finding	Interval
Small rectal hyperplastic polyps (Except "Serrated Polyposis Syndrome")	10 y
1-2 tubular adenomas < 1 cm with only low-grade dysplasia	5-10 y
Serrated polyp without dysplasia	5 y
3 to 10 adenomas or serrated polyps (SP);	3 y
Any "Advanced Adenoma" (>/= 1 cm, or villous, or high-grade dysplasia), or Serrated Polyp with dysplasia, or Traditional Serrated Polyp, removed completely (no piecemeal)	3 y
> 10 adenomas or serrated polyps (SP) (consider familial syndrome)	1 y
Sessile adenoma removed piecemeal	2-6 months

Additional Surveillance Considerations

- Discontinuation of surveillance should be considered in patients with serious comorbidities with less than 10 years of life expectancy.
- Surveillance guidelines are intended for asymptomatic people; new symptoms may need diagnostic work-up.
- Evolving technologies like chromoendoscopy, magnification endoscopy, narrow band imaging, and CT colonography are not established for postpolypectomy surveillance at this time.

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

Guidelines for Colonoscopy Surveillance After Cancer Resection: A Consensus Update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer

Rex DK, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, Burt RW, Byers T, Fletcher RH, Hyman N, Johnson D, Kirk L, Lieberman DA, Levin TR, O'Brien MJ, Simmang C, Thorson AG, Winawer SJ

Candidates for Surveillance

- After surgical resection of Stage I, II, III colon and rectal cancer
- After curative-intent resection of Stage IV cancers
- After endoscopic resection of Stage I
- **Patients with unresectable cancer generally not candidates for surveillance**

Goals of Postcancer-Resection Surveillance

- **Detection of Surgically Curable Recurrence of primary CRC:**
  - Annual CXR and CT of Liver
  - Serial CEA, if pre-op was high (?)
- **Detection of metachronous neoplasm:**
  - Main goal in colon CA prevention
  - Colonoscopy surveillance

Goals of Postcancer-Resection Surveillance

- **Surveillance to identify anastamotic recurrence in <u>rectal</u> cancer:**
  - High rates of local recurrence
  - Proctoscopy and Rectal EUS
- **In RCTs or meta-analyses: Detection of local recurrence of primary colon cancer tumor (anastamotic recurrence) by annual or more frequent C-scope does not confer any survival benefit**

Postcancer Resection Surveillance Recommendations

1. Patients with colon and rectal cancer should undergo **high-quality perioperative clearing of synchronous lesions** (usually "clearing colonoscopy").
   - **In nonobstructing tumors:**
     - preoperative colonoscopy to cecum.
   - **In obstructing colon cancers:**
     - CT colonography with intravenous contrast or
     - Double-contrast barium enema
   - If no unresectable metastases found during surgery :
     - Colonoscopy to clear the colon of synchronous disease 3 to 6 months after the resection, OR
     - Colonoscopy performed intraoperatively

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

Postcancer Resection Surveillance Recommendations

2. Patients undergoing curative resection for colon or rectal cancer should undergo a repeat colonoscopy to detect "early metachronous" lesions:
   - 1 year after the resection (+ pre-op clearing), OR
   - 1 year after the "clearing colonoscopy"

   This colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumors.

3. If the examination performed at 1 year is normal, then:
   - interval before next colonoscopy should be 3 years.
   - if "3-year post clearing" colonoscopy is normal, the subsequent examination should be in 5 years.

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

Postcancer Resection Surveillance Recommendations

4. Following the examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy

5. Periodic examination of the rectum to identify local recurrence, at 3- to 6-month intervals for the first 2 or 3 years, may be considered after low anterior resection of rectal cancer. Techniques:

   - rigid/flexible proctoscopy, or
   - rectal endoscopic ultrasound.

   These examinations are independent of the colonoscopic examinations described above for detection of metachronous disease.

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Post-Colorectal Cancer Surveillance

	Interval from Previous Exam
Clearing Colonoscopy	Before, During, or 3 months After Resection
Post-Clearing Colonoscopy	1 year later
1st Metachronous Surveillance	3 years later
Subsequent Metachronous Surveillance	5 years later, and every 5 years thereafter

Rectal Cancer

Local Recurrence Surveillance After Low-Anterior Resection

(In addition to Colonoscopies)

	Interval	Duration
Rectal EUS or Rigid/Flexible Proctoscopy	Every 3 months	3 years

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

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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)

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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**

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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**

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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

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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

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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

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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;

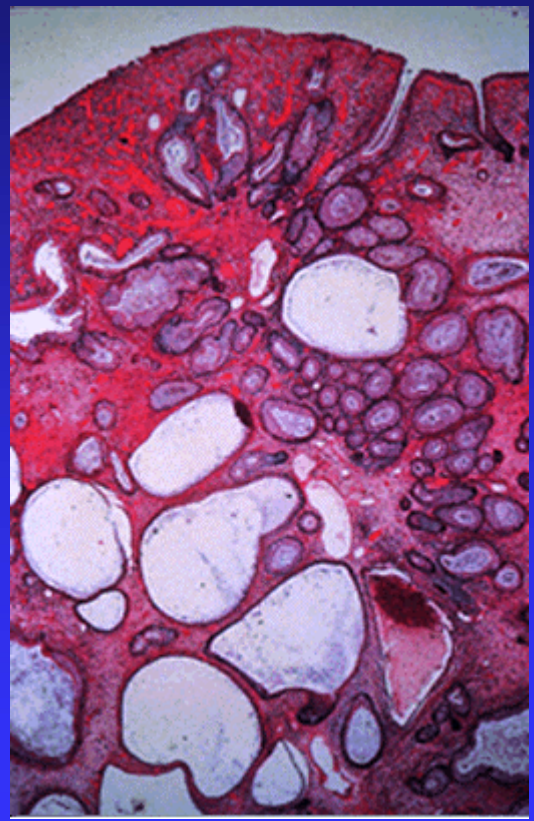
  mammography annually (alternative – MRI);

  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

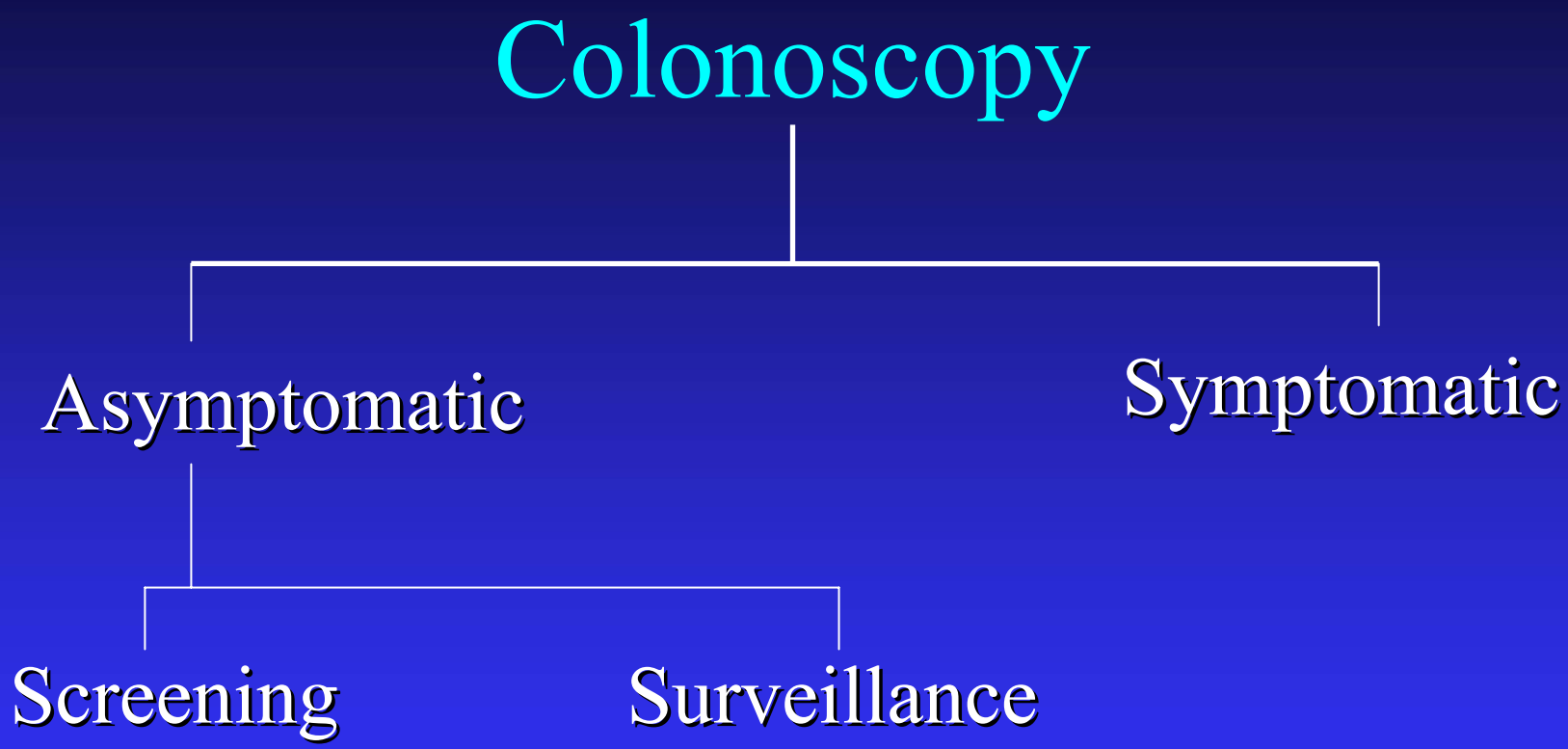
Familial Juvenile Polyposis



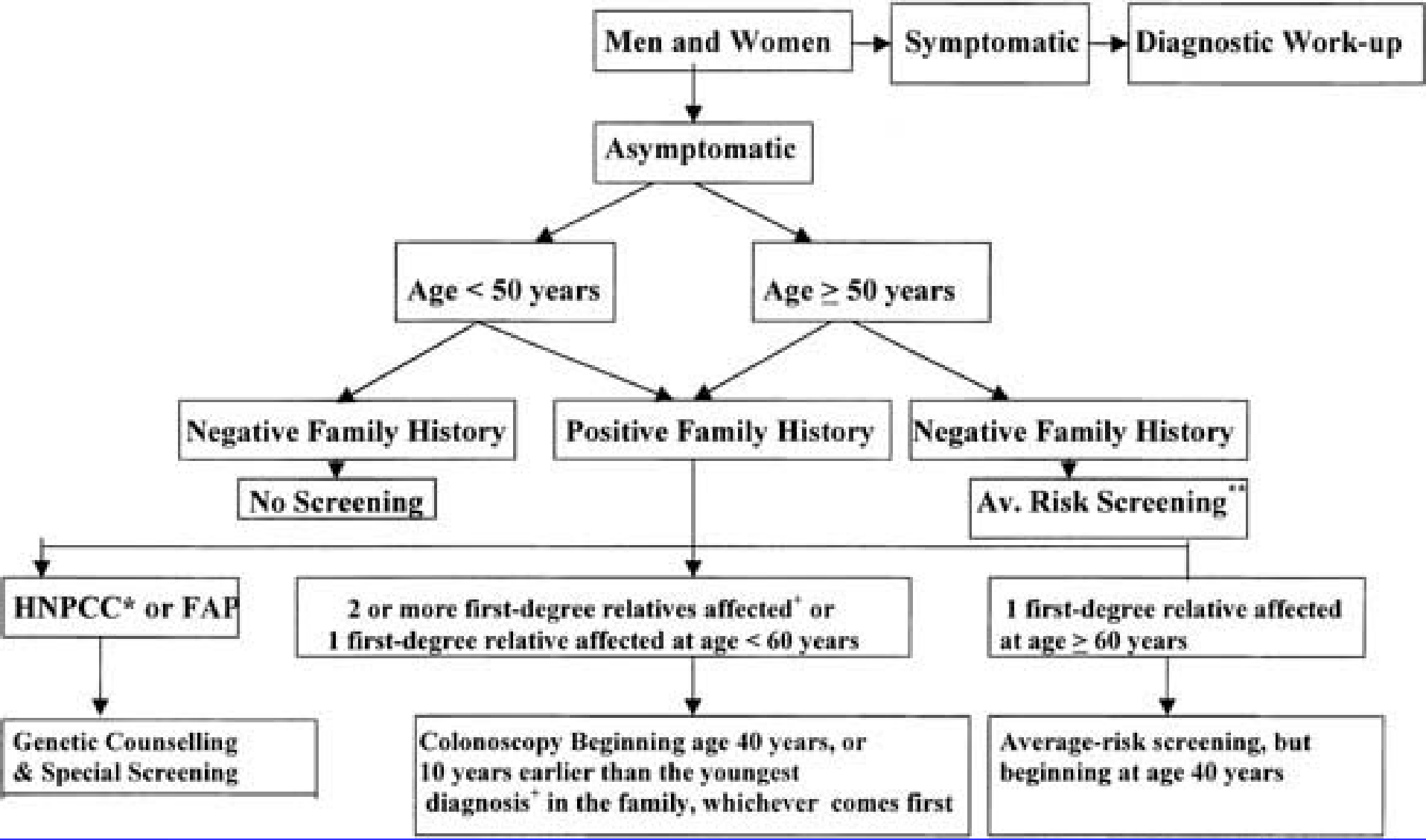
Familial Juvenile Polyposis – Surveillance and Screening

- 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



Gastroenterology- 2003 (Vol. 124, Issue 2: 1865-1871)

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 ?