Colorectal Cancer 101

Djenaba A. Joseph, MD, MPH
Medical Director, Colorectal Cancer Control Program
Division of Cancer Prevention and Control
National Center for Chronic Disease Prevention and Health Promotion
Centers for Disease Control and Prevention

Facts About Colorectal Cancer

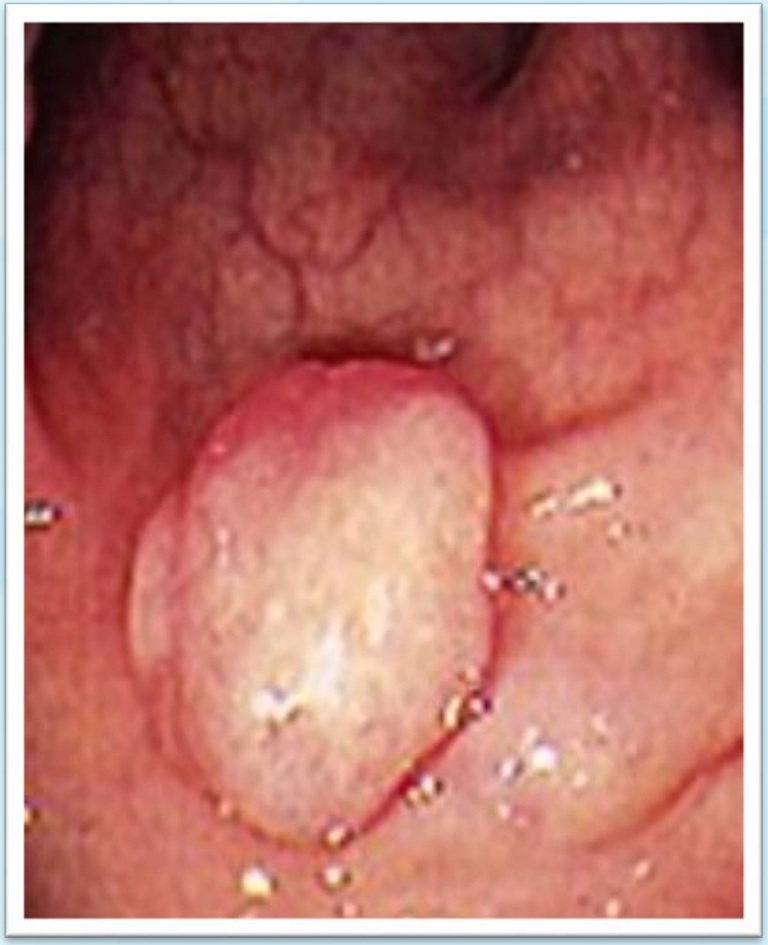
- **130,607 new cases and 52,045 deaths in 2010 in the United States***
- **2nd leading cause of cancer death overall, after lung cancer**
- **Can be prevented or detected early through screening**
- **Colorectal cancer incidence and mortality have been declining in the United States**
  - 30% decrease in incidence during past decade among adults aged 50 and older**
- **Screening has been an important contributor to U.S. declines in incidence and mortality**

*U.S. Cancer Statistics Working Group. 2013. Available here.

**Siegel R et al. CA Cancer J Clin 2014;64:104-117.

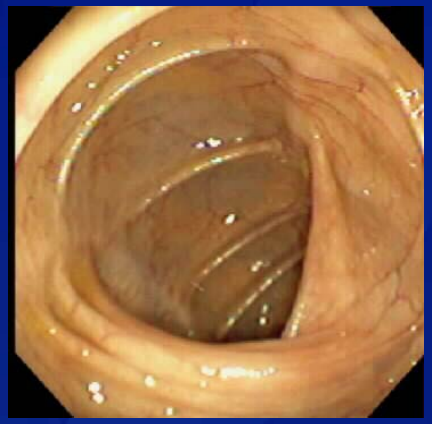
Where Does Colorectal Cancer Come From?

- Most cancers of the colon and rectum develop over years from adenomatous or serrated polyps
- Polyps are very common and increase with age but very few progress to cancer
- Polyps that are larger, have dysplasia, or villous histology have a higher risk of progression to cancer than other polyps
- Estimate of polyp dwell time from a <1 cm adenomatous polyp to an invasive cancer is at least 10 years

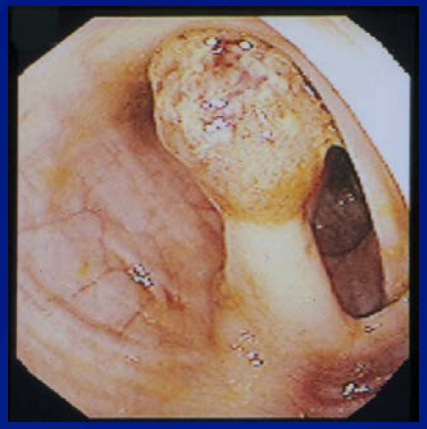


Natural History of Colorectal Cancer

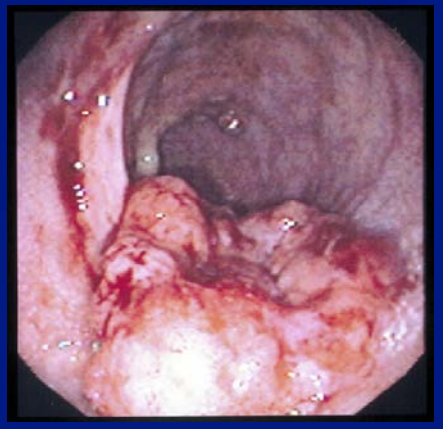
Normal

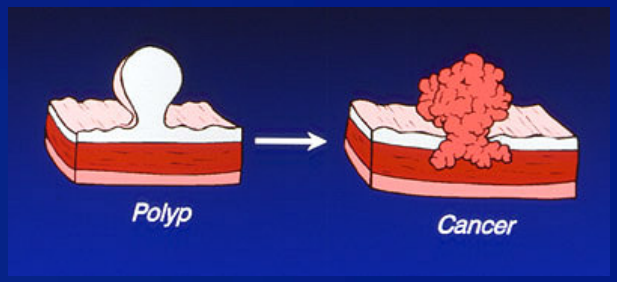


Polyp



Adenocarcinoma





How Colorectal Cancer Screening Works

Screening tests are performed *before* a person has symptoms

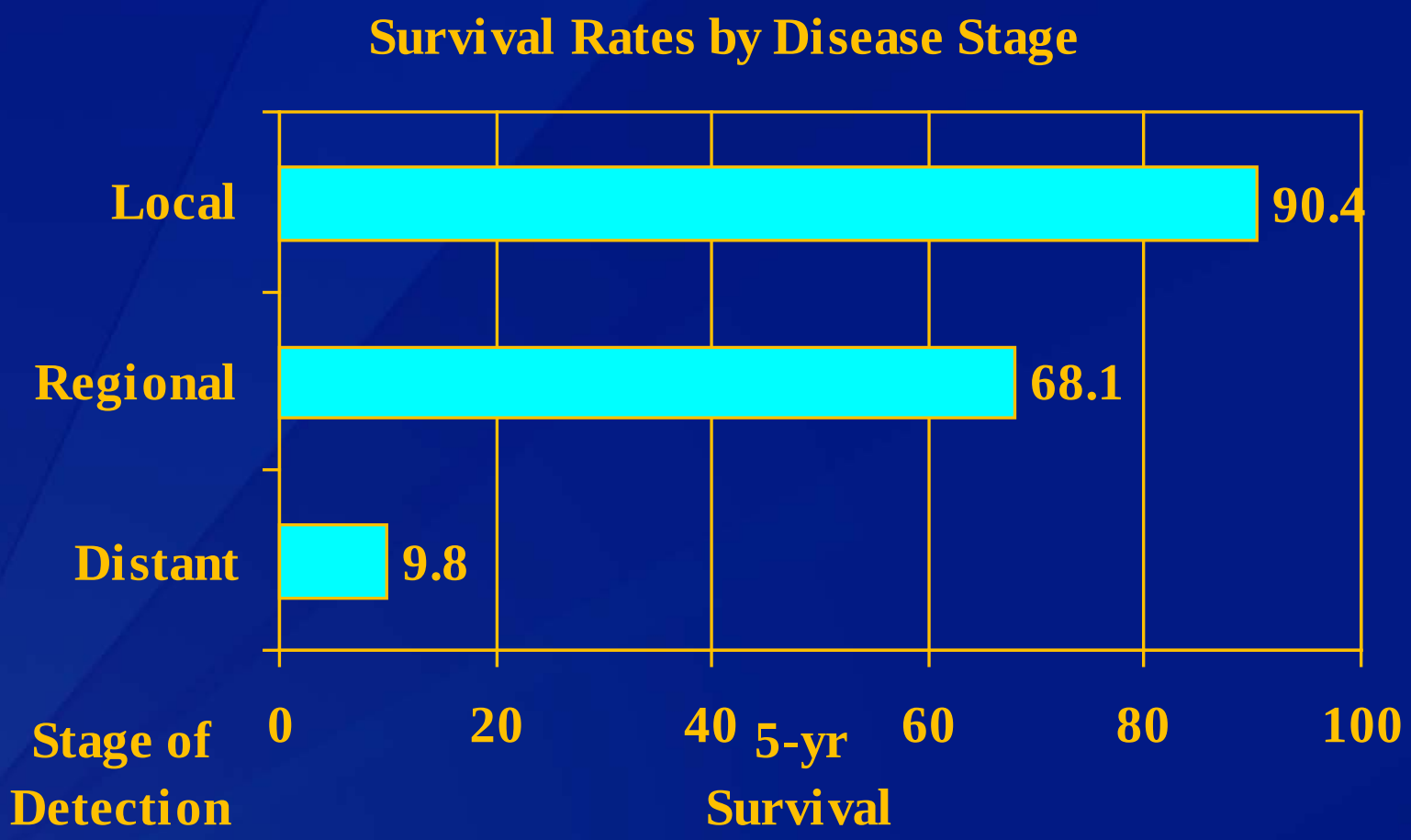
- To detect a disease or disease precursor which may be present but silent
- To prevent or more effectively treat the disease

Colorectal Cancer Screening = Prevention & Early Detection

Prevention (polyp removal) → Decreased Incidence

Early Detection → Decreased mortality

Benefits of Screening



Source: SEER Cancer Statistics Review, 1975-2003

Is Screening Appropriate for Your Patient?

Need to know patient's:

- Risk level
- Screening and surveillance history
- Age
- Comorbidities
- Preferences

Risk Stratification to Ensure Appropriate Screening and Surveillance*

- **Average Risk**
  - No signs or symptoms of CRC
  - None of the risk factors below
- **Increased Risk**
  - Family history of CRC or adenomas in a first-degree relative or CRC in two second-degree relatives
  - Personal history of adenomas, certain serrated polyps, or CRC
- **High Risk**
  - Inflammatory bowel disease: chronic ulcerative colitis or Crohn's colitis
- **Highest Risk**
  - Confirmed or suspected genetic syndromes (FAP, HNPCC)

*Diagnostic testing is appropriate for patients with signs or symptoms

Screening for Colorectal Cancer

AVERAGE RISK

Patients at Average-Risk: Screening Guidelines

Three Screening Options:

- High-sensitivity guaiac-based FOBT (HS-gFOBT) or fecal immunochemical tests (FIT) yearly, or
- Flexible sigmoidoscopy every 5 years with interval HS-gFOBT or FIT every 3 years, or
- Colonoscopy every 10 years

US Preventive Services Task Force. Ann Intern Med. 2008;149(9):627-37.

Summary USPSTF Recommendations

Population	Grade	Recommendation	Rationale
Age 50-75 years	A	Screen routinely with HS-FOBT, sigmoidoscopy, or colonoscopy	Benefits of screening outweigh potential harms
Age 76-85 years	C	Do not screen routinely	Likelihood that detection and early intervention yields a mortality benefit declines after age 75 due to time lag between adenoma development and cancer diagnosis
Age >85 years	D	Do not screen	

USPSTF Test/Interval Recommendations

Screening Test	Grade	Interval	Rationale
High sensitivity FOBT (guaiac or immunochemical)	A	Annual	All are effective in decreasing CRC mortality. Risks and benefits of screening methods vary.
Flexible sigmoidoscopy	A	Every 5 years with HS-FOBT every 3 years	
Colonoscopy	A	Every 10 years	
CT colonography	I	N/A	Insufficient evidence to assess benefits and harms
Fecal DNA	I	N/A	

Rationale

- **Cancer Intervention and Surveillance Modeling Network (CISNET)**
  - Microsimulation modeling
  - Compared life-years gained relative to resource use for different screening strategies
- **Adults age 76 – 85 years**
  - Gain in life years small in comparison to risks
  - Assumes all previous screens for CRC negative
  - Benefit of screening not seen for 7 years
- **Adults age >85 years**
  - Competing causes of mortality

FOBT Based Strategy

- **Annual High-sensitivity FOBT**
  - Required fewest colonoscopies
  - Hemeoccult Sensa
  - FIT with similar characteristics as Magstream quantitative tests
  - Hemeoccult II did not have similar effectiveness
    - Fewer life-years gained
    - Lower predicted incidence/mortality reduction

Endoscopy Based strategies

- **Sigmoidoscopy every 5 years with HS FOBT every 3 years**
  - Sigmoidoscopy alone did not have similar effectiveness
    - Fewer life-years gained
    - Lower predicted incidence/mortality reduction
  - Minimal decrease in life-years gained compared to sigmoidoscopy every 5 years with annual FOBT
- **Colonoscopy every 10 years**

Should African Americans Start Screening Before Age 50?

Recommendation: begin screening at age 50

- **Rationale for earlier screening:**
  - Higher age-specific rates of CRC among African Americans
- **Rationale against earlier screening:**
  - Most CRC cases in African Americans occur after age 60
  - Prevalence of polyps >9mm similar for whites and African Americans
  - No evidence supporting effectiveness of earlier screening
  - Increasing screening rates by >10% among African Americans over age 50 more effective than earlier screening
- **Guidelines vary:**
  - USPSTF, ACS-MSTF-ACR*: age 50
  - ACG**, ASGE***: age 45
  - ACP: age 40
- **Coverage varies:**
  - Medicare and states with mandatory screening requirement: age 50

*ACS-MSTF-ACR: American Cancer Society –Multi-Society Task Force on Colorectal Cancer – American College of Radiology
**ACG: American College of Gastroenterology
***ASGE: American Society for Gastrointestinal Endoscopy

Screening and Surveillance for Colorectal Cancer

INCREASED RISK

Screening Patients with a Family History

- **If patient has either:**
  - CRC or adenomas* in a first –degree relative diagnosed at **age ≥60** OR
  - Two second-degree relatives with CRC

Begin screening at age 40 with any test recommended for average-risk; repeat at usual intervals based on type of test and findings**

- **If patient has either:**
  - CRC or adenomas* in a first-degree relative diagnosed **before age 60** OR
  - Two or more first-degree relatives diagnosed at any age (with family history not suggestive of genetic syndrome)

Colonoscopy every 5 years, starting at age 40 or 10 years before the youngest case in the family was diagnosed, whichever comes first**

*Our expert opinion is that this applies to relatives with advanced adenomas only, i.e., adenomas that are > 1cm, villous, or with high-grade dysplasia, recognizing that this information is often unavailable.

**The evidence base for these guidelines was not strong and some aspects are controversial.

Levin B et al. CA Cancer J Clin. 2008; 58(3):130-160.

Surveillance of Patients with Adenomas at Prior Colonoscopy

- **Low risk adenomas***
  - 1-2 tubular adenomas <10mm

→ Colonoscopy in 5-10 years

- **High risk adenomas***
  - 3-10 adenomas <10mm OR
  - ≥1 adenoma ≥10mm OR
  - ≥1 adenoma with villous features OR
  - ≥1 adenoma with high grade dysplasia

→ Colonoscopy in 3 years

  - >10 adenomas

→ Colonoscopy in <3 years (consider syndrome)

- **Any adenoma with piecemeal or possibly incomplete excision**

→ Colonoscopy in 2-6 months

*These recommendations assume that the prior colonoscopy was complete and adequate.

For serrated polyps, see here

Lieberman DA et al. Gastroenterology 2012; 143: 844-57.

CRC SCREENING TESTS

Test Options

- **Stool based tests**
  - Guaiac fecal occult blood tests (gFOBT or FOBT)
  - Immunochemical FOBT (iFOBT or FIT)
  - mtsDNA (multi-target stool DNA)
- **Endoscopic tests**
  - Flexible sigmoidoscopy
  - Colonoscopy
- **Radiology**
  - Double contrast barium enema
  - CT colonography or virtual colonoscopy

Guaiac FOBT vs FIT

- gFOBT
  - Detects peroxidase activity of heme
  - In presence of heme and developer (hydrogen peroxide), guaiac acid turns blue
  - Heme present in red meat, fruits, vegetables (radishes, turnips, broccoli)
  - Vitamin C inhibits guaiac reaction
- FIT
  - Specific antibodies to hemoglobin
  - Specific to bleeding from colon (globin does not survive passage through UGI)
  - No dietary restriction
  - Unaffected by medications
  - Quantitative
  - Automated developers and readers

Fecal Immunochemical Tests (FIT)

gFOBT: Test Characteristics

	Hemeoccult II	Hemeoccult Sensa
Percent test positive	2.5%	10% - 13.6%
Sensitivity CRC	25% - 38%	64% - 80%
Specificity CRC	98% - 99%	87% - 90%
Sensitivity adenoma ≥10 mm	16% - 31%	41% - 68.6%
Specificity adenoma ≥10 mm	~91%	87% - 91%

Whitlock EP, Lin JS, Liles E, et al. Screening for colorectal cancer: a targeted systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:638-658.

gFOBT: Evidence

	Mandel, 1993	Mandel, 1999	Hardcastle, 1996	Kronborg, 1996
Frequency of Testing	Annual	Biennial	Biennial	Biennial
Duration (years)	18	18	8	13
Slide rehydration	Yes	Yes	No	No
% requiring colonoscopy	30%	30%	5%	5%
Mortality reduction	33%	21%	15%	18%
Incidence reduction	20%	17%		

Mandel JS, Bond JH, Church TR, et al. N Engl J Med 1993; 328: 1365-71.
Mandel JS, Church TR, Ederer F, Bond JH. J Natl Cancer Inst 1999;91:434-7.
Hardcastle JD, Chamberlain JO, Robinson MH, et al. Lancet 1996; 348:1472-1477.
Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard. Lancet 1996; 348:1467-1.

FIT Test Characteristics

Condition Detected	Sensitivity	Specificity
Cancer	68.8% 90.9%	94.4% 95.6%
Advanced adenomas	22.2% 40.3%	97.4% 91.3%

Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: an updated systematic review for the review for the U.S. Preventive Services Task Force. AHRQ Publication No. 14-05203-EF-1. Oct 2015.

Caveats

- **FITs for which there is good evidence may or may not be the same as FITs currently marketed**
  - Sample collection (1, 2, or 3 days)
  - Sample collection method (stick, brush, tests per stool, sample stability, sample transport)
  - Sensitivity/specificity for qualitative FITs depends on cutpoint
- **Mortality reduction depends on program of annual FOBT**
  - Test sensitivity vs Program sensitivity
- **Positive FOBTs must be followed up with colonoscopy**
  - DO NOT REPEAT POSITIVE FOBTs
  - If colonoscopy negative, next screen in 10 years

Step 1: Select an Effective Test

- **Not all FITs have been rigorously tested**

Criterion for choosing a FIT:

- Use a FIT that has been evaluated in clinical practice and for which data on performance in the peer-reviewed literature show at least 50% sensitivity for cancer

Step 1: Select an Effective Test

- **A brand of FIT that has been extensively tested and is available in the United States is OC FIT-CHEK® (Polymedco):**
  - Provided as a 1-sample kit in most cases. The collection method involves inserting the probe several times into the stool to a point on the probe just above the ridges and placing the collection probe into a small tube. The stool is probed before it comes into contact with the toilet water.
  - Test processing can be manual or automated
    - Manual: OC-Light®* – point-of-care assay
      - Estimated sensitivity for cancer: 93% (95% CI, 83%-97%)
    - Automated: OC-Auto®* – uses an automated analyzer

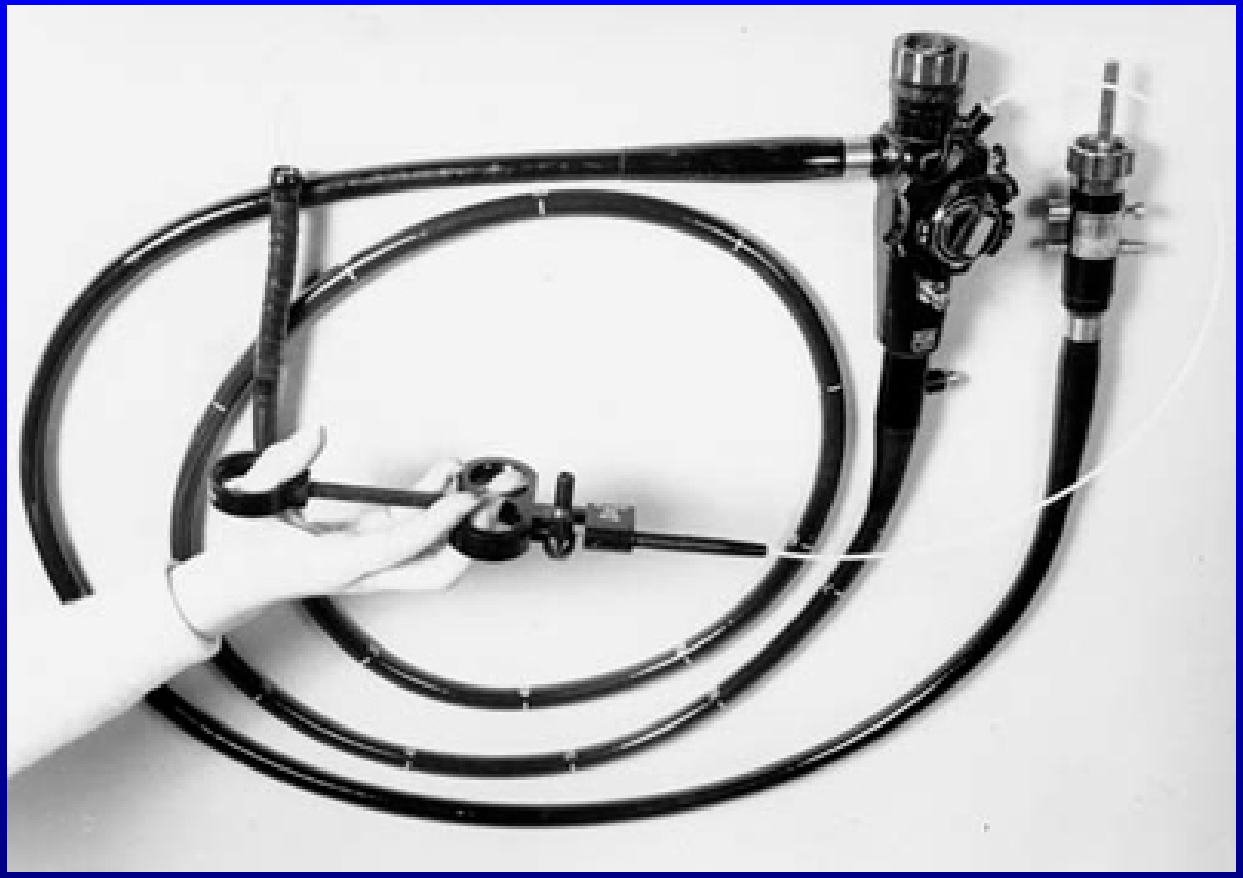
Lee JK et al. Ann Intern Med. 2014:160:171-181.

*Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services

FIT/FOBT

- Advantages
  - Inexpensive
  - Does not require specialized resources
  - Test can be done at home
  - FIT specific for human blood
  - No dietary restrictions with FIT
  - Proven CRC mortality reduction with gFOBT
- Disadvantages
  - Annual testing
  - Dietary restriction for gFOBT
  - Uncertain cost benefit over time
  - Decreased sensitivity for adenomas (? Prevention of CRC)
  - FIT test variation

Colonoscopy



Colonoscope

Colonoscopy

Adenoma	Sensitivity
≥6 mm	74.6% - 92.8%
≥10 mm	89.1% - 94.7%

Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: an updated systematic review for the review for the U.S. Preventive Services Task Force. AHRQ Publication No. 14-05203-EF-1. Oct 2015.

Colonoscopy: Evidence

- **USPSTF: Insufficient evidence to provide precise estimates of sensitivity in community setting**
  - Lack of true gold standard
  - Sensitivity estimates from tandem CTC studies
- **Indirect evidence**
  - Observational studies: 60% - 90% reduction in CRC incidence after polypectomy
  - National Polyp Study
    - 76% - 90% reduction observed CRC incidence over 6 years

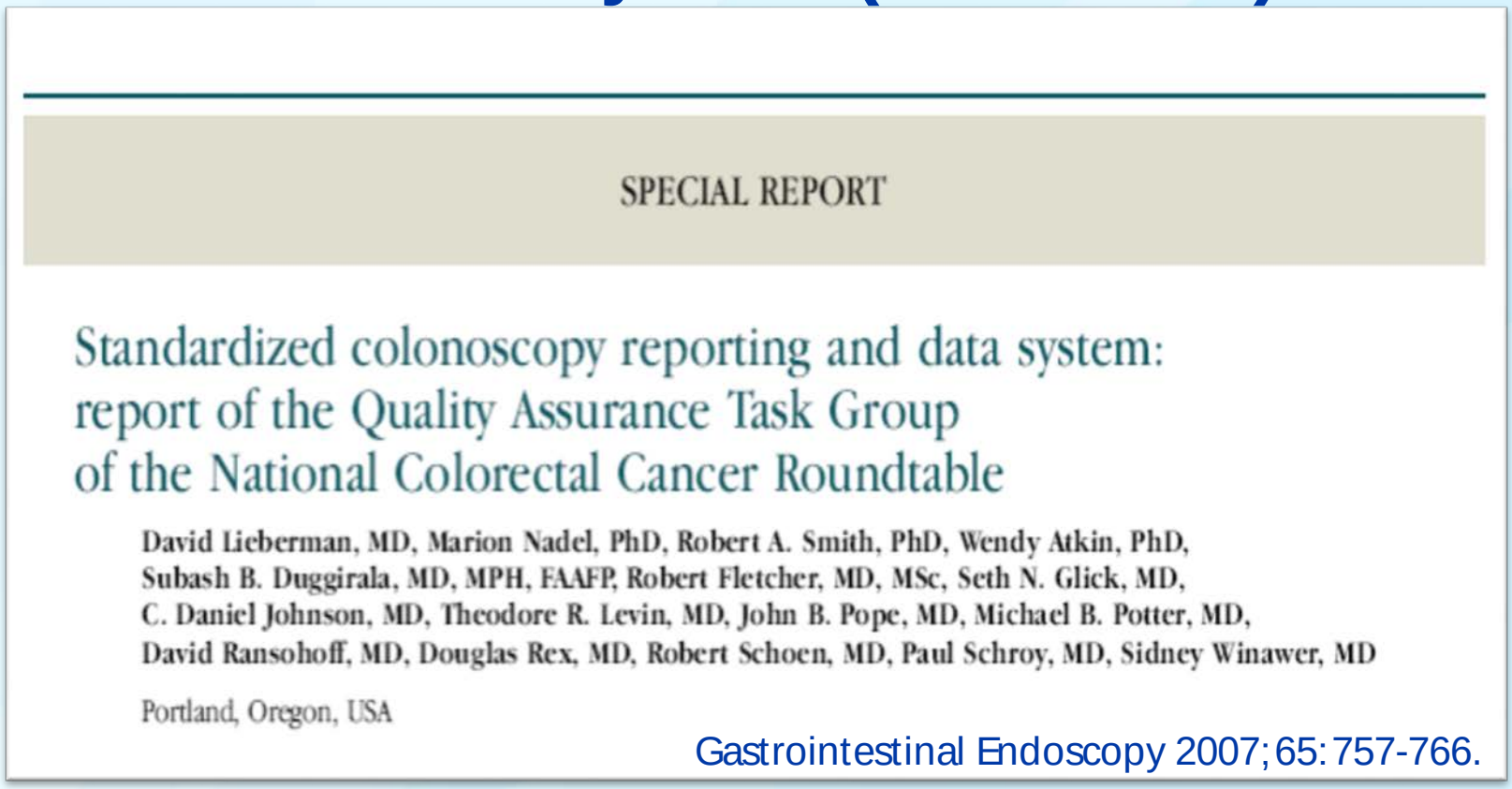
Colonoscopy Caveats

- **Some contradictory evidence**
  - 3 U.S. chemoprevention trials
    - Incidence CRC after clearing colonoscopy 4x that seen in NPS
    - No reduction CRC incidence
  - 2 U.S. dietary intervention trails
    - Higher rates incident CRC after clearing colonoscopy than NPS
- **Effectiveness dependent on quality**
  - Variable performance due to skill level of endoscopist
- **Complications**
  - Serious complications 2.8 per 1,000 procedures (perforations, hemorrhage, CV events, severe abdominal pain, death)

Colonoscopy

- Advantages
  - Most accurate test as single application
  - Detection and removal of polyps in single procedure
  - If negative, once every 10 years
- Disadvantages
  - Bowel preparation
  - Sedation (requires transportation and time off work)
  - Invasive
  - Complications
  - Expensive
  - Missed adenomas, interval cancers

Standardized Colonoscopy Reporting and Data System (CO-RADS)



SPECIAL REPORT

Standardized colonoscopy reporting and data system: report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable

David Lieberman, MD, Marion Nadel, PhD, Robert A. Smith, PhD, Wendy Atkin, PhD, Subash B. Duggirala, MD, MPH, FAAFP, Robert Fletcher, MD, MSc, Seth N. Glick, MD, C. Daniel Johnson, MD, Theodore R. Levin, MD, John B. Pope, MD, Michael B. Potter, MD, David Ransohoff, MD, Douglas Rex, MD, Robert Schoen, MD, Paul Schroy, MD, Sidney Winawer, MD

Portland, Oregon, USA

Gastrointestinal Endoscopy 2007;65:757-766.

http://www.giejournal.org/article/S0016-5107(07)00003-X/fulltext

5. Monitor Procedure Quality - Assessing the Endoscopist

Indicators of endoscopist procedure quality:

- Adenoma Detection Rate (ADR)
- Cecal intubation rate
- Quality of bowel preparation
- Use of appropriate intervals for screening and surveillance

5. Monitor Procedure Quality – Adenoma Detection Rates

- **Definition: The percent of screening exams with at least one adenoma detected**

CURRENT TARGET*

ADR should be: ≥25%: male screening patients

≥15%: female screening patients

*These benchmarks may increase with additional data

- **Probably the most important quality indicator**
  - Multiple studies have demonstrated that the rate of subsequent development of CRC is inversely related to the endoscopist's ADR (Kaminski et al. 2010, Corley et al. 2014)

5. Monitor Procedure Quality – Cecal Intubation Rates

- Definition: percent of exams in which the cecum was reached

TARGET

All exams: >90%

Screening and surveillance exams: >95%

- Important lesions can be missed if colonoscopy is not complete to the cecum
- Failure to reach the cecum constitutes an incomplete exam

5. Monitor Procedure Quality – Bowel Prep Adequacy Rates

- Monitor the percent of patients with bowel prep quality adequate to detect lesions >5mm

TARGET

≥90% good-excellent or adequate

- Poor bowel prep results in missed lesions and need to repeat exam sooner, increasing risk and cost
- If <90% of exams are good, practice should be examined and remediated

Flexible Sigmoidoscopy

Fiberoptic sigmoidoscope

CDC
SAFER·HEALTHIER·PEOPLE™

Flexible Sigmoidosocpy

- **Test characteristics**
  - Estimated sensitivity for CRC throughout entire colon: 58% - 75%
  - Estimated sensitivity for advanced neoplasia: 72% - 86%
  - Isolated proximal advanced neoplasia: 0.8% - 3.2% in average risk population
- **Adenoma miss rate**
  - 20% overall polyps any size (14.% polyps ≥10mm, 19% ≥6mm)
- **Refer for colonoscopy if adenoma found**
  - Risk proximal adenoma 2x greater with adenoma any size in distal colon
  - If no biopsy, refer for polyp >5mm

Flexible Sigmoidoscopy: Evidence

- **Case control studies**
  - Selby[1]
    - Rigid sigmoidoscopy with polypectomy
    - 60% reduction in mortality from distal CRC over 10 years
    - Death from proximal cancers same in both groups
  - Newcomb[2]
    - 79% mortality reduction for CRC with reach of sigmoidoscope
- **Randomized control trial**
  - Atkin[3] (UK trail)
    - One time flex sig between age 55-65 years
    - Incidence CRC in people attending screening reduced 33%
    - CRC mortality reduced 43%
    - Incidence distal CRC reduced 50%

[1] Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. N Engl J Med 1992; 326:653-7.

[2] Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. J Natl Cancer Inst 1992; 84:1572-5

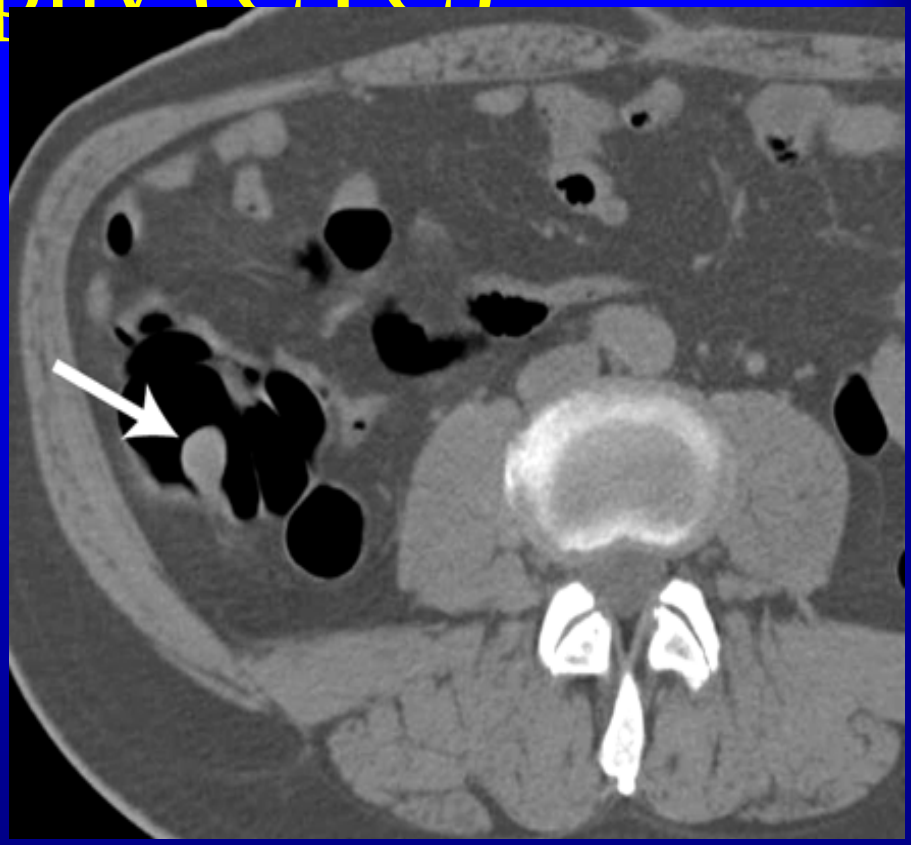
3 Atkin WS, Edwards R, Kralj-Hans I, et al. Once only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised control trial. Lancet 2010;375:1624-33.

Flexible Sigmoidoscopy

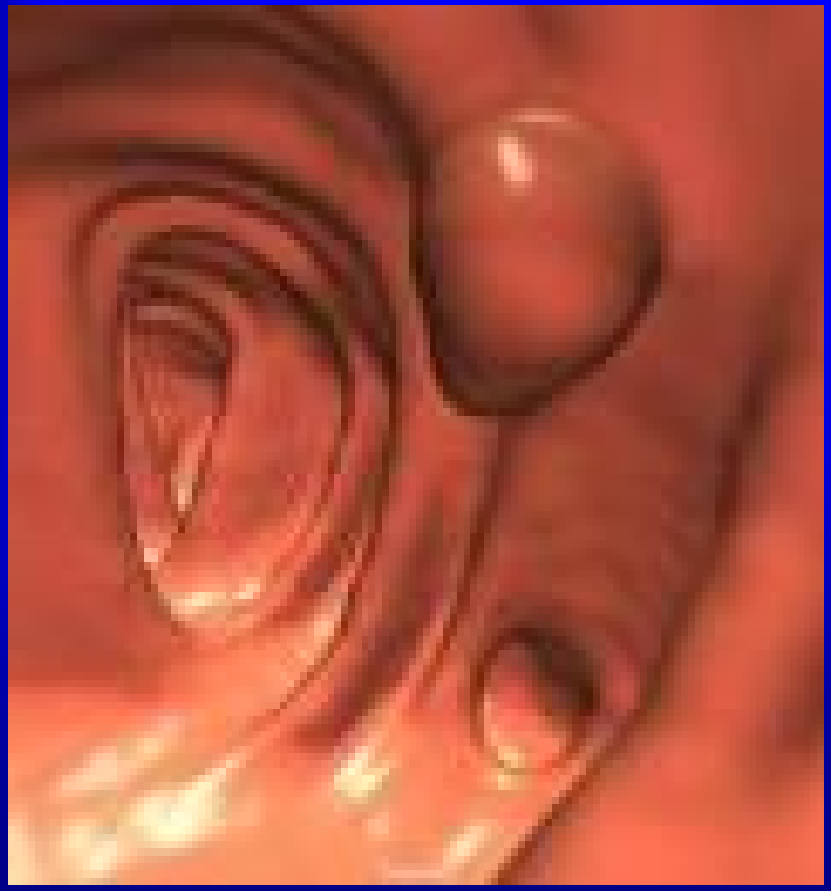
- Advantages
  - Office based
  - Does not require sedation
  - Simplified bowel preparation
  - Every 5 years
  - Evidence to support incidence/mortality reduction
- Disadvantages
  - Complications
  - Quality
  - Invasive
  - May miss isolated proximal adenomas/cancers

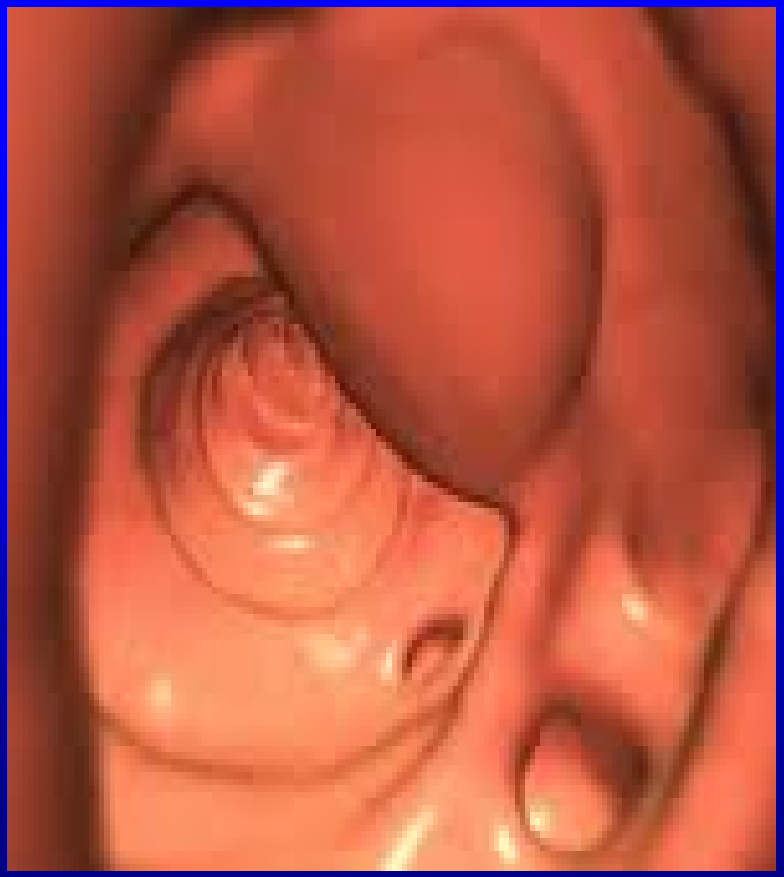
Computed Tomographic Colonography (CTC)

- Single detector CT
  - Slice selection determined before study
  - Fixed
- Multidetector CT
  - Range of possible slice thickness
  - Post-study
  - Thinner slices
  - Shorter time



3D CTC





CT Colonography: Test characteristics

	Pickhardt[1]	ACRIN[2]	Kim[3]	Johnson[4]
Sensitivity				
CRC	2 of 2 cases	6 of 7 cases	None	5 of 5
Adenoma ≥10mm	93.8%	90%	100%	50-83%
Adenoma ≥6mm	88.7%	78%	59-77%	NR
Specificity				
Adenoma ≥10mm	96%	86%	99-100%	97-99%
Adenoma ≥6mm	79.6%	88%	89-99%	NR
Colonoscopy referral rate				
Adenoma ≥10mm	1 in 13	NR	1 in 10	Not calc
Adenoma ≥6mm	1 in 3	1 in 6-8	1 in 5	Not calc

1. Pickhardt PJ, Choi JR, Hwang I, et al. NEJM 2003;349:2191-200
2. Johnson CD, Chen, MH, Toledano AY, et al. NEJM 2008;359:1207-17
3. Kim SH, Lee JM, Eun HW, et al. Radiology 2007;244:852-64
4. Johnson CD, Fletcher JG, MacCarty RL, et al. . AJR Am J Roentgenol 2007;189:672-80

CT Colonography: Uncertainties

- Radiation exposure
- Extracolonic findings
  - 40-70%
  - 5% - 37% need diagnostic follow-up
  - 3% need definitive treatment
- Community vs. research setting
- Management of small polyps
- Sensitivity for flat adenomas
- Professional capacity/training
- Test interval

mtsDNA

- Cologuard
- Tests stool for:
  - presence of known DNA alterations in adenoma-carcinoma sequence
  - Human hemoglobin with FIT
- Requires entire stool specimen (30 g minimum)
- Sensitivity CRC 92.3% (vs 73.8 FIT alone)
- Specificity 84.4% (higher false positive rate)

DRAFT USPSTF 2015 Recommendations

Population	Recommendation	Grade (What's This?)
Adults ages 50 to 75 years	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary.	A
Adults ages 76 to 85 years	The decision to screen for colorectal cancer in adults ages 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history. • Adults in this age group who have never been screened for colorectal cancer are more likely to benefit. • Screening would be most appropriate among adults who: 1) are healthy enough to undergo treatment if colorectal cancer is detected, and 2) do not have comorbid conditions that would significantly limit life expectancy.	C

Draft: Table. Recommended Screening Strategies for Colorectal Cancer

Screening Modality	Frequency*	Other Considerations
FIT or high-sensitivity gFOBT	Every year	Requires the fewest lifetime colonoscopies (a proxy for harms). Does not require bowel cleanout, anesthesia, or transportation to and from the screening examination (test is performed at home).
Flexible sigmoidoscopy with FIT	Flexible sigmoidoscopy every 10 years plus FIT every year	Potentially attractive option for persons who want endoscopic screening but wish to limit exposure to colonoscopy. May also be useful when access to colonoscopy is geographically limited.
Colonoscopy	Every 10 years	Requires less frequent screening. Screening and diagnostic followup of positive results can be performed during the same examination.

* Applies to persons with negative screening tests (including hyperplastic polyps) and is not intended for those in surveillance programs.

Abbreviations: FIT=fecal immunochemical test; gFOBT=guaiac-based fecal occult blood test.

Bottom Line

The best test is the one that gets done

Free CME

- http://www.cdc.gov/cancer/colorectal/quality/index.htm

Questions?
dajoseph@cdc.gov

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov