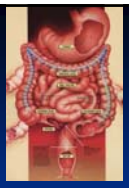
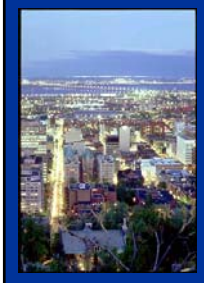



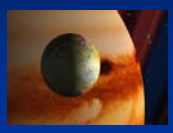

The Means and Evidence for Colorectal Cancer Screening

Montreal, Quebec
October 2006




Jack Mandel, PhD, MPH
Emory University

Incidence of Cancer Worldwide, 2002



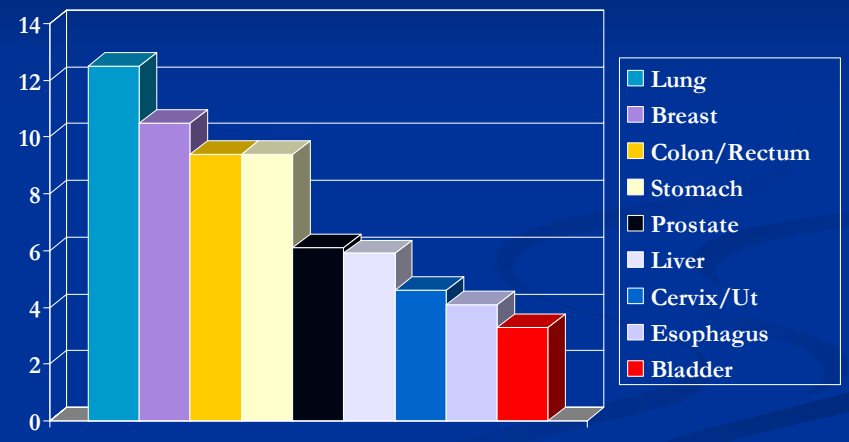

- 11 million new cancer cases
- 7 million cancer deaths
- 25 million people living with cancer

- One million CRC cases
- 500,000 CRC deaths
- Lifetime risk about 6 - 7%

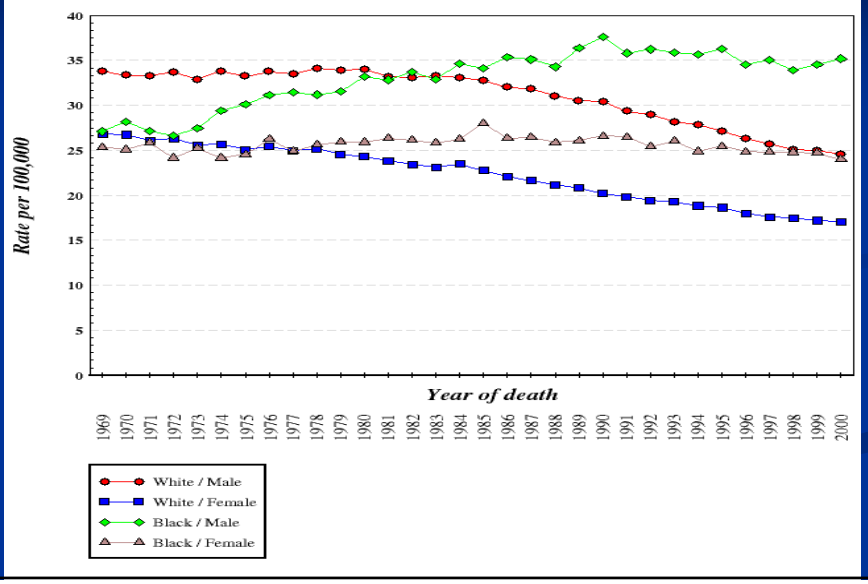
Cette présentation a été effectuée le 27 octobre 2006, au cours du Symposium "La santé publique et le dépistage du cancer : espoirs et réalités" dans le cadre des Journées annuelles de santé publique (JASP) 2006. L'ensemble des présentations est disponible sur le site Web des JASP, à l'adresse http://www.inspq.qc.ca/jasp.

Incidence of Cancer Worldwide

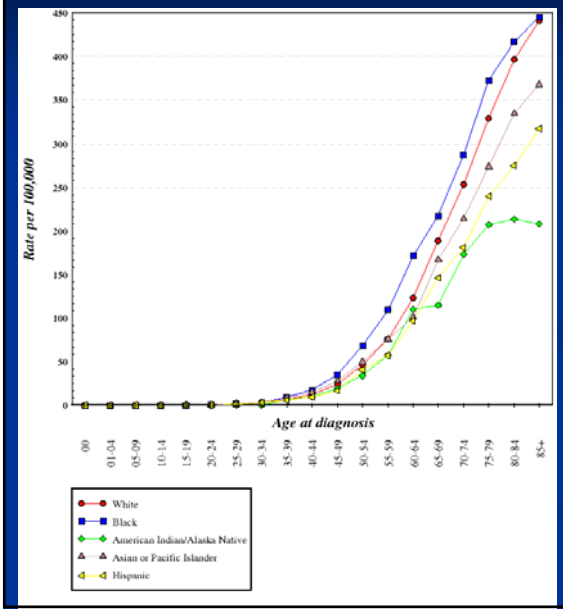
Percent by site



Age-Adjusted *Mortality* by Gender and Race, USA



Age Specific Colorectal Cancer Incidence Rates by Race, SEER, 1998-2002

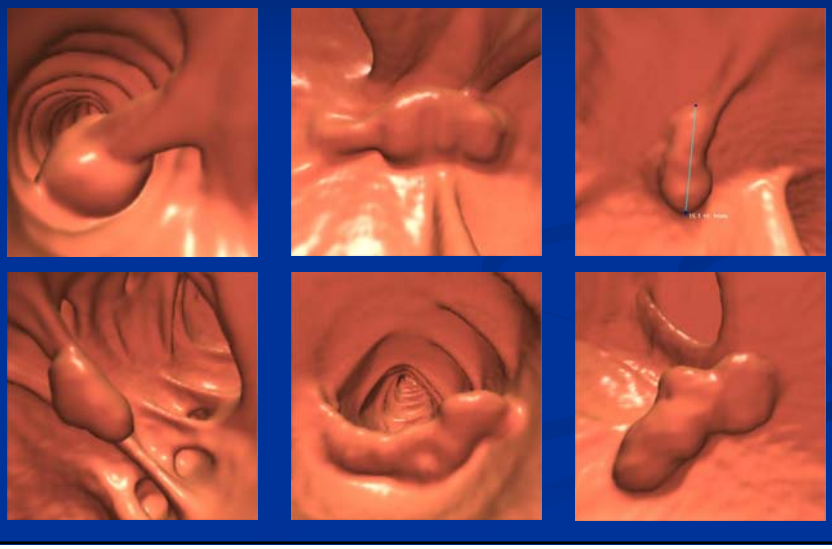


- CRC increases with age
- Most CRC is diagnosed after age 60
- Beginning at age 50 there is the potential to detect cancers and significant polyps

Goal of Cancer Prevention

- To prevent cancer from occurring
- When it does, diagnosis it as early as possible or identify a precursor lesion

Adenoma



Establishing the **Strategic Framework**
for the **Canadian Strategy for Cancer Control**

Canadian Strategy for Cancer Control

Statement of Endorsement: Population-Based Colorectal Cancer Screening

Position

The Council of the Canadian Strategy for Cancer Control has reviewed the recommendations made by the National Committee on Colorectal Cancer Screening (NCCCS), an Expert Panel supported by Health Canada, which included members from provinces and key organizations from across the country. To access the report, please go to: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/nccs-cndcc/ccsrec_e.html.

The Council fully endorses and supports the NCCCS's recommendations that include the need for provinces to develop and implement high quality, population-based colorectal cancer screening programs. Their recommendation is based on strong clinical trial evidence, which supports that fecal occult blood screening could reduce colorectal cancer mortality by 15–33% in a targeted population of 50–74 year olds.

Based on this evidence, the Council further supports the National Committee's recommendations that:

- Screening be offered to all Canadians aged 50-74 years using unrehydrated Hemoccult II or equivalent as the entry test.
- Individuals be screened at least every two years
- Positive tests be followed up by colonoscopy, with options of barium enema and flexible sigmoidoscopy where appropriate.

Screening Guidelines in USA

Since 1997 published screening guidelines have generally recommended a number of options

One message has been that colonoscopy can detect advanced neoplasms which might not be detected by other tests

The Media Speaks
The Katie Couric Effect

Katie's first colonoscopy

It's considered the most effective test for detecting colon cancer, and as Katie Couric says in her special report, "It really didn't hurt."

American Cancer Society Guidelines for CRC Screening of Average Risk Adults Age 50+

- Guaiac or immunochemical fecal occult blood test (*g*FOBT or *i*FOBT) annually 
- Flexible sigmoidoscopy (FSIG) every 5 yrs 
- FOBT annually + FSIG every 5 yrs
- Colonoscopy every 10 yrs 
- Double contrast barium enema every 5 yrs 

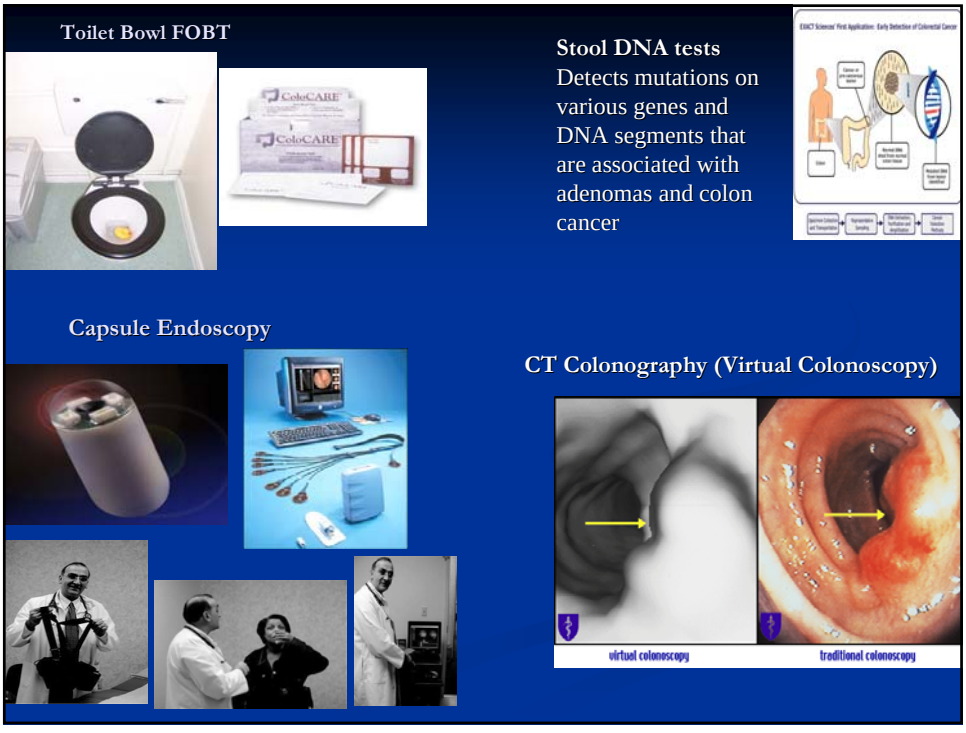
- *All positive tests should be followed up with colonoscopy

ACS 2003 CRC Screening Guidelines Technology Update

TESTS *NOT* RECOMMENDED FOR SCREENING

- Toilet-bowl *g*FOBT
- Single sample FOBT following digital rectal exam in the doctor's office
- Stool DNA test
- CT colonography
- Capsule endoscopy

Courtesy of Robert Smith, ACS



There are many screening tests for CRC but only one has been proven to be effective

Very strong evidence from randomized controlled clinical trials for *g*FOBT

Randomized Controlled Trials of FOBT

	Minnesota	Nottingham	Funen
Yr. Started	1975	1981	1985
Number	46,551	152,850	61,933
Age	50 – 80	45 – 74	45 – 75
Test	Hemoccult	Hemoccult	Hemoccult II

Randomized Controlled Trials of FOBT

	Minnesota	Nottingham	Funen
CRC Mortality Reduction (%)			
Annual	33*		
Biennial	21*	15*	18*
Compliance(Av. %)	75	50	57
Follow-up (yrs)	18	8	10

Burgundy, France Study

- Randomized geographic areas not individuals
- 91,199 individuals aged 45-74 years
- 6 screening rounds with Hemoccult and colonoscopy of test positives
- No dietary restrictions
- 11 years of follow-up
- Compliance: 53% first test, 54-58% for subsequent screens
- Positivity: 2.1% on first screen, 1.4% on average later screens
- Results: Mortality Ratio=***0.84*** (.71-.99) and 0.67 (.56-.81) for those who participated at least once

The Minnesota Trial
Compliance With Screening

Completed at least one screen	90%
Completed at least 50% of screens	80%
Completed 100% of screens	50%

10% did not complete any screens

The Minnesota Trial
Compliance With Diagnostic Protocol

82% of test positives received adequate diagnostic examination

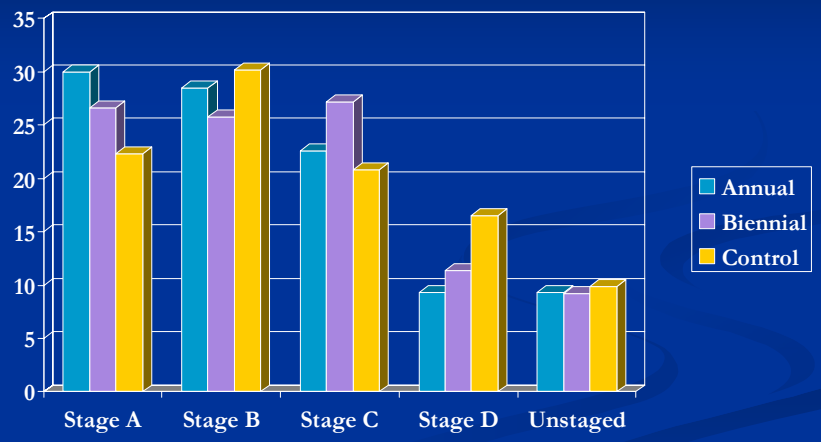
The Minnesota Trial

With 100 percent
compliance the colorectal cancer
mortality reduction
might have been greater than
the observed reduction.

Results from Randomized Trials

	Percent Reduction In CRC Mort.	Percent Average Compliance
Minnesota		
Annual	**33**	**75**
Biennial	**21**	**75**
Nottingham	**15**	**50**
Funen	**18**	**57**
Goteborg	**12**	**62**
Burgundy	**16**	**55**

CRC by Study Group and Dukes Stage, Minnesota Study



Hemoccult II v. Hemoccult SENSA

Author, year and Study Population	FOBT	%Pos	Se*	Sp*	PPV*
Rozen, 1997 – those attending screening clinic (97%) + symptomatic patients	H II Sensa	6.0 8.7	63 63	95 92	21 14
Greenberg 2000 – patients at 9 centers requiring colo for symptoms, family hx or polyp surveillance	H II Sensa	9.4 11.4	38 47	94 93	42 44
Allison 1996 – screen >50 yrs of age at Kaiser Permanente	H II Sensa	2.5 13.6	32 71	98 88	23 9
Castiglione, 1992 – referral patients	H II Sensa	4.8 5.6	-	-	18 16
Petrelli, 1994 – 39000 test kits with 2 tests distributed free in NY; 23% returned	HII Sensa	5.1 9.5	-	-	18 16
For cancer or adenoma 1+ cm					

*g*FOBT

- Not specific for colorectal bleeding
- Detects heme peroxidase activity and are not specific for human hemoglobin peroxidase in feces. Hemoglobin from red meat, peroxidase from fruits and vegetables, and certain medications can cause false-positive reactions and need to be avoided for several days before the test.
- Test is non-invasive and specimens can be collected at home
- Unsuitable for automated mass development
- Fecal sampling process is awkward

*i*FOBT

InSure

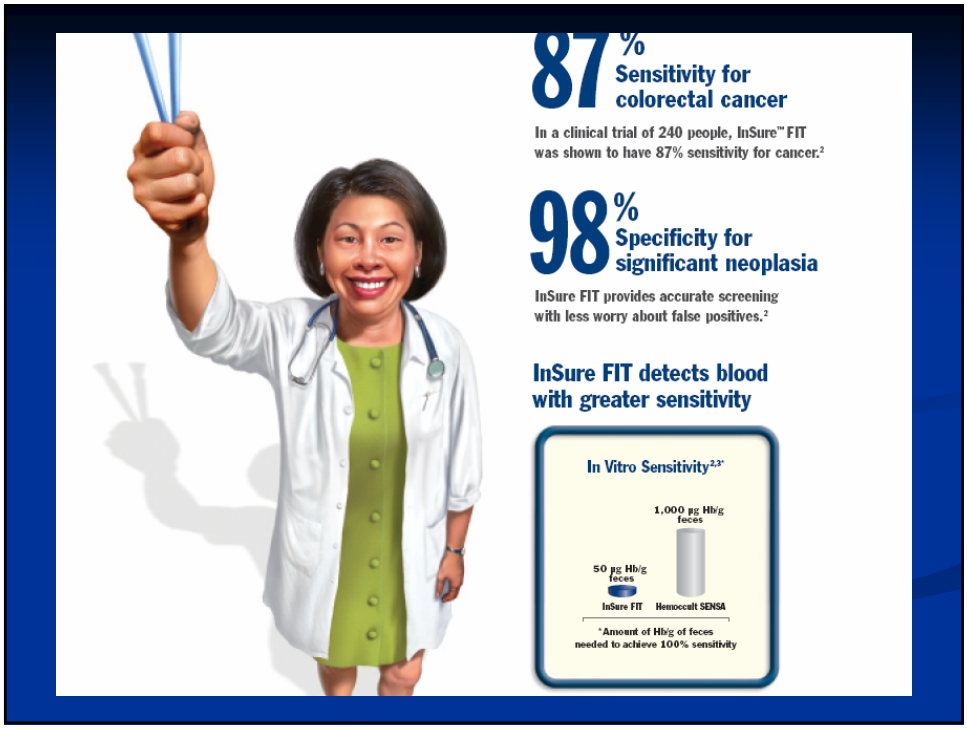
Fecal Immunochemical Test

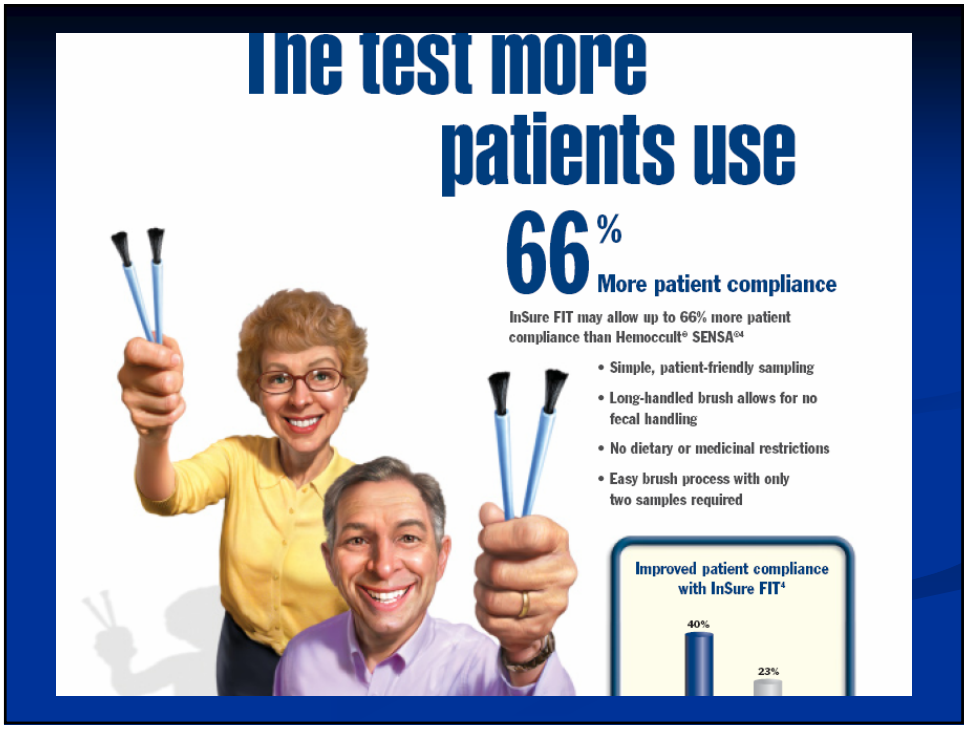
Saved by the brush

Simple, Sensitive, Specific

*i*FOBT

- Does not react with non-human hemoglobin or peroxidase, so food restrictions are not necessary.
- Are more specific for lower GI bleeding
- ***Lift the flap on bar coded test card and dab with specimen***
- ***Brush over surface of immersed stool. Close flap & seal. Repeat with next stool. Mail in reply-paid envelope to lab for development***
- Can be developed by technicians or can automate the development


87%
Sensitivity for colorectal cancer
In a clinical trial of 240 people, InSure™ FIT was shown to have 87% sensitivity for cancer.[2]
98%
Specificity for significant neoplasia
InSure FIT provides accurate screening with less worry about false positives.[2]
InSure FIT detects blood with greater sensitivity
In Vitro Sensitivity[2,3]*
1,000 µg Hb/g feces
50 µg Hb/g feces
InSure FIT
Hemoccult SENSA
*Amount of Hb/g of feces needed to achieve 100% sensitivity


The test more patients use
66%
More patient compliance
InSure FIT may allow up to 66% more patient compliance than Hemoccult® SENSA®[4]
• Simple, patient-friendly sampling
• Long-handled brush allows for no fecal handling
• No dietary or medicinal restrictions
• Easy brush process with only two samples required
Improved patient compliance with InSure FIT[4]
40%
23%

Summary – *i*FOBT versus *g*FOBT

- **Performance/acceptance advantages:**
  - *i*FOBT appears to be more sensitive and more specific than *g*FOBT
  - *i*FOBT is selective for colorectal bleeding
  - For iFOBT there is no need for diet or drug restrictions
  - Compliance appears to be higher with *i*FOBT
- Processing advantages:
  - Quantifiable
  - Automated
  - Distribution, reporting, reminders can be automated

Studies comparing *g*FOBT to *i*FOBT

- There have been about 15 studies that met following criteria:

  -published in peer reviewed journal
  -described study population
  -at least 80% of enrollees participated
  -performed diagnostic exam on test+
  -did not rehydrate *g*FOBT
  -reported results for cancer, adenoma larger than 1 cm or both combined

And we found

- Generally, *i*FOBT "performed better"
- More similar for cancer but *i*FOBT better for adenomas

Screening Colonoscopy

"Colonoscopy every 10 years is the preferred screening strategy for average-risk persons age 50 and older if they have no risk factors for colorectal cancer other than age."

Recommendation by the American College of Gastroenterology(ACG)

Screening Colonoscopy

- Considered to be the "best" screening test
- The risk of serious complications is 1 in 300
- This risk must be weighed against the benefit which has not been established
- There are not enough practitioners to provide a skilled colonoscopic examination for all eligible U.S. citizens
- Less qualified examiners could absorb the overflow but the increased inaccuracy and complications need to be considered against the benefit

Seef LC, Manninen DL, et al. *Gastroenterology* 2004; 127:1661-1669.
Levin TR, Editorial *Gastroenterology* 2004; 127:1841-1849.
Lieberman, DA, et al. *N Engl J Med* 2000; 343:162-8.

What do we know?

- Most polyps do not lead to death from CRC
  - Only about 2.5/1000 polyps per year progress to cancer
  - Large polyps (>1cm) become colorectal cancers at a rate of roughly 1% per year
  - A large polyp left in situ has a cumulative risk of malignancy at 20 years of 24%
  - The development of invasive cancer from a small (<10mm) adenoma is extremely unlikely in less than five years
  - "Because most polyps, even the advanced ones, do not directly lead to death from CRC, the most important value of one test over another is the incremental benefit of mortality reduction that the test confers to the patient being screened. If screening tests other than colonoscopy are used as directed, the incremental benefit of colonoscopy is small"

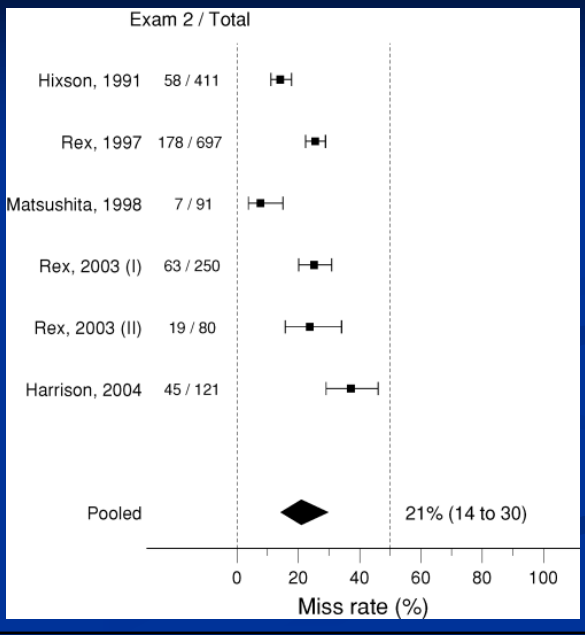
Allison J and Lawson M. Screening tests for colorectal cancer: a menu of options remain relevant. Curr Oncol Rep 2006;8:492-8

Polyp Miss Rates Based on "Tandem" or "Back-to-Back" Colonoscopy*

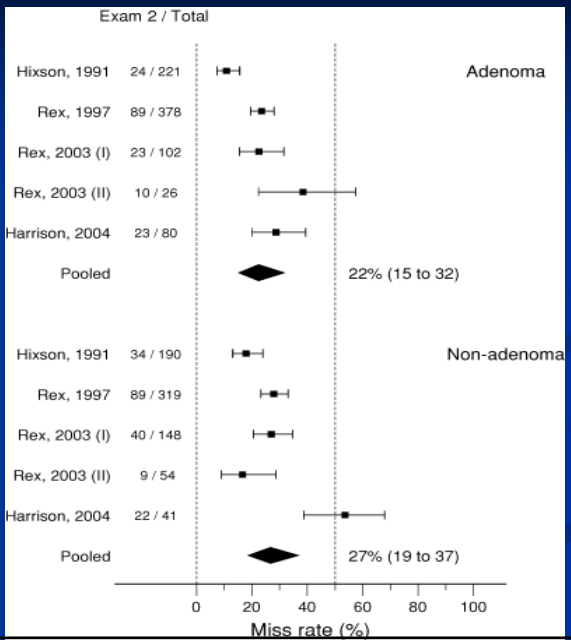
- 6 studies involving 465 patients, aged 37-92
- Cecum reached in 88-100% of patients
- Total of 1650 polyps
- Pooled miss rate was 21%
- Miss rate higher for nonadenomatous polyps (27%) compared to adenomatous polyps (22%)
- Miss rate higher for adenomas 1-5mm (26%) than for adenomas 10+mm (2%)

Van Rijn et al. Am J Gastroenterol 2006;101:343-350

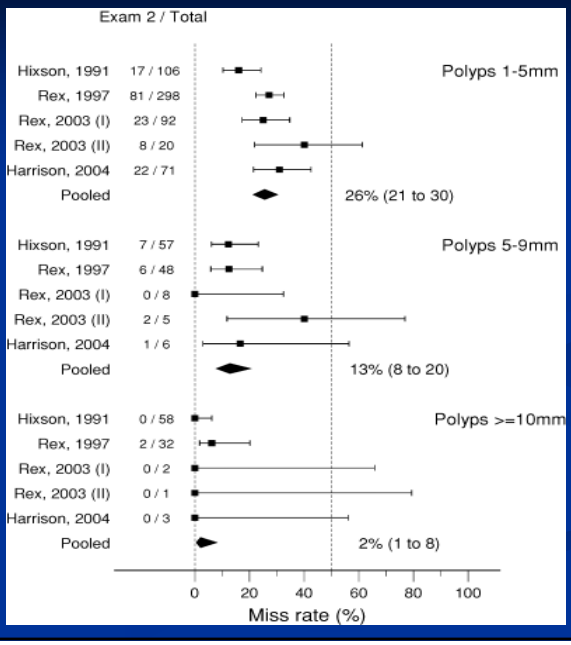
Miss rate of all polyps

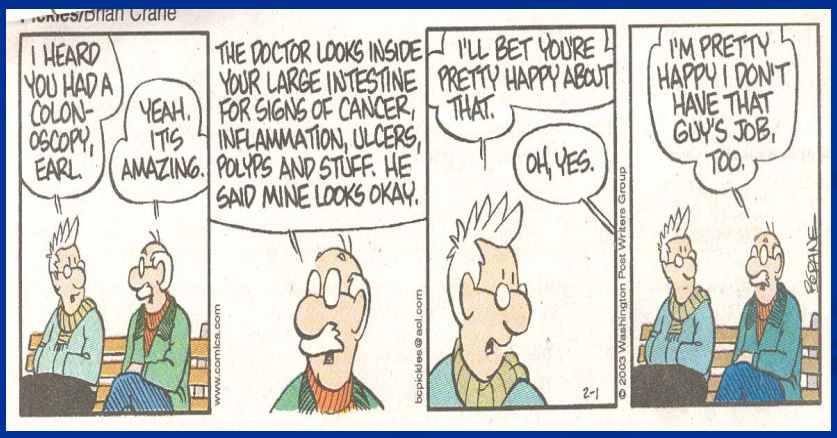


Polyp miss rate by type



Adenoma miss rate by size





Virtual Colonoscopy

NEJM 2003;349:2191-200

Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults

Perry J. Pickhardt, M.D., J. Richard Choy, Sc.D., M.D., Inku Hwang, M.D., James A. Butler, M.D., Michael L. Puckett, M.D., Hans A. Hildebrandt, M.D., Roy K. Wong, M.D., Pamela A. Nugent, M.D., Pauline A. Mysliwiec, M.D., M.P.H., and William R. Schindler, D.O.

The NEW ENGLAND JOURNAL of MEDICINE

DECEMBER 4, 2003

Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults

ABSTRACT

Multi-center screening trial of 1,233 asymptomatic adults

Table 3. Performance Characteristics of Virtual Colonoscopy and Optical Colonoscopy for the Detection of Adenomas.*

Variable	Size Category				
	≥6 mm	≥7 mm	≥8 mm	≥9 mm	≥10 mm
	no./total no. (% [95% CI])				
Analysis according to patient					
Virtual colonoscopy					
Sensitivity	149/168 (88.7 [82.9–93.1])	100/110 (90.9 [83.9–95.6])	77/82 (93.9 [86.3–98.0])	53/57 (93.0 [83.0–98.1])	45/48 (93.8 [82.8–98.7])
Specificity	848/1065 (79.6 [77.0–82.0])	981/1123 (87.4 [85.3–89.2])	1061/1151 (92.2 [90.5–93.7])	1116/1176 (94.9 [93.5–96.1])	1138/1185 (96.0 [94.8–97.1])
Accuracy	997/1233 (80.9 [78.6–83.0])	1081/1233 (87.7 [85.7–89.5])	1138/1233 (92.3 [90.7–93.7])	1169/1233 (94.8 [93.4–96.0])	1183/1233 (95.9 [94.7–97.0])
Test-positive rate†	366/1233 (29.7 [27.1–32.3])	242/1233 (19.6 [17.4–22.0])	167/1233 (13.5 [11.7–15.6])	113/1233 (9.2 [7.6–10.9])	92/1233 (7.5 [6.1–9.1])
Sensitivity of optical colonoscopy	155/168 (92.3 [87.1–95.8])	100/110 (90.9 [83.9–95.6])	75/82 (91.5 [83.2–96.5])	51/57 (89.5 [78.5–96.0])	42/48 (87.5 [74.8–95.3])
Analysis according to polyp					
Sensitivity of virtual colonoscopy	180/210 (85.7 [80.2–90.1])	119/133 (89.5 [83.0–94.1])	88/95 (92.6 [85.4–97.0])	56/61 (91.8 [81.2–97.3])	47/51 (92.2 [81.1–97.8])
Sensitivity of optical colonoscopy	189/210 (90.0 [85.1–93.7])	120/133 (90.2 [83.9–94.7])	85/95 (89.5 [81.5–94.8])	55/61 (90.2 [79.8–96.3])	45/51 (88.2 [76.1–95.6])

* The data for optical colonoscopy are for the initial optical colonoscopy performed before the results on virtual colonoscopy were revealed. CI denotes confidence interval.
† Data are for the virtual colonoscopic studies that were deemed to be positive in each size category.

Results

- 1233 asymptomatic adults, age 50-79 from 3 centers underwent both exams
- Prevalence of adenomatous polyps:

  10+mm= 3.9%

  6+mm=13.6%

Results

	Sensitivity for Adenomas(%)	
	6+mm	10+mm
Virtual	89	94
Optical	92	88

VC is comparable to OC for clinically important lesions

CT COLONOGRAPHY TEST CHARACTERISTICS:per polyp

(At least 100 patients)

Study, Year	No. Patients	Sensitivity (Percent) Polyps 6+ mm	Polyps 10+mm
Arnesen, 2005	100	54	67
Rockey, 2005	614	60	64
Iannaccone, 2004	203	80	100
Cotton, 2004	600	23	52
Macari, 2004	186	46	91
Van Gelder, 2004	249	77	78
Pickhardt, 2003	**1233**	**89**	**94**
Iannaccone, 2003	158	83	100
Johnson, 2003	703	47	46
Pineau, 2003	205	75	78
Pedersen, 2003	144	73	92
Yee, 2003	182	80	93
Laghi, 2002	165	82	92

CT COLONOGRAPHY TEST CHARACTERISTICS(per patient)

Study	N	Polyps 6-9 mm			Polyps >1cm			All polyps	Cancer	All polyps
		Se %	Sp %	PPV%	Se %	Sp %	PPV%	Se %	Se %	Sp %
Arnesen, 2005	100	60	91	53	75	96	69	61	0	61
Rockey 2005	614	51	-	-	59	96	63	55	78	89
Cotton, 2004	600	*30*	*93*	39	55	96	50	21	75	91
Van Gelder,2004	249	-	-	-	84	*92*	60	62	-	31
Iannaccone,2004	203	87	-	-	100	100	100	90	*100*	92
Pickhardt, 2003	1233	87	83	*38*	94	96	49	89	*100*	80
Johnson, 2003	703	52	91	39	*48*	98	62	-	-	-
Pineau, 2003	205	84	*83*	59	90	95	64	62	-	71
Pederson, 2003	144	82	-	-	96	-	-	-	-	-
Lefere, 2002	100	91	92	78	*100*	*100*	100	86	-	-
Yee, 2001	300	93	-	-	*100*	-	-	90	100	72
Hara, 2001	237	-	-	-	68	96	49	-	-	-
Fletcher, 2000	180	-	-	-	85	93	93	88	*72*	89
Fenlon, 1999	100	*94*	92	*92*	96	96	96	82	100	84

Flexible Sigmoidoscopy

- There are a number of ongoing trials

Flexible Sigmoidoscopy

- But no results
- Evidence from case-control studies indicates a benefit from flexible sigmoidoscopy screening
- Some studies compared the diagnostic yield (advanced adenoma - >1 cm – and cancer) of FS v. FOBT
- Yield is higher with FS
- Usually a one time FOBT

DNA Tests

Agrawal J, Syngal S. **Colon cancer screening strategies**. Current Opin Gastroenterol 2004;21:59-63

- FOBTs limited because of intermittent bleeding
- Advantage of DNA as marker is that it is shed continuously

Author	Overall sensitivity of assay	Sensitivity by molecular alteration*	Sensitivity by tumor stage†‡	Sensitivity by tumor location§	Specificity
Syngal *et al.* [22••], 2004	43/68 (63%) for CRC 6/23 (26%) for adenoma	K-ras 20/91 (22%) p53 13/91 (14%) APC 17/91 (19%) Bat-26 6/91 (7%) L-DNA 20/91 (22%)	TNM I 7/18 (39%) TNM II 14/20 (70%) TNM III 21/29 (72%) TNM IV 1/1 (100%) HGD adenoma 4/12 (33%) LGD adenoma 2/11 (18%)	Proximal 15/39 (38%) Distal 34/52 (65%)	No controls
Calistri *et al.* [20], 2003	33/53 (62%)	K-ras 6/53 (11%) p53 3/53 (6%) APC 1/53 (2%) MSI 3/53 (6%) L-DNA 27/53 (51%)	Dukes A 1/4 (25%) Dukes B 10/19 (53%) Dukes C 15/22 (68%) Dukes D 3/3 (100%)	Proximal 5/13 (38%) Distal 24/35 (69%)	37/38 (97%)
Tagore *et al.* [21••], 2003	33/52 (63%) for CRC 16/28 (57%) for adenoma	K-ras 17/80 (21%) p53 19/80 (24%) APC 11/80 (14%) Bat-26 2/80 (3%) L-DNA 26/80 (33%)	TNM I 18/24 (75%) TNM II 8/12 (67%) TNM III 5/12 (42%) TNM IV 2/4 (50%) HGD adenoma 6/7 (86%) LGD adenoma 10/21 (48%)	Sensitivity data not presented by location; 90% of lesions studied were distal	204/212 (96%)
Rengucci *et al.* [19], 2001	12/46 (26%)	K-ras 6/46 (13%) p53 3/46 (7%) MSI 3/46 (7%)	Dukes A 0/4 (0%) Dukes B 4/19 (21%) Dukes C 6/20 (30%) Dukes D 2/3 (67%)	No data on tumor location presented	18/18 (100%)
Dong *et al.* [18], 2001	36/51 (71%)	K-ras 8/48 (17%) p53 30/51 (59%) Bat-26 3/51 (6%)	Dukes A 1/1 (100%) Dukes B 14/17 (82%) Dukes C 14/21 (67%) Dukes D 7/12 (58%)	Proximal 11/14 (79%) Distal 25/37 (68%)	No controls
Ahlquist *et al.* [17], 2000	20/22 (91%) for CRC 9/11 (82%) for adenoma	K-ras 5/33 (15%) p53 3/33 (9%) APC 8/33 (24%) Bat-26 5/33 (15%) L-DNA 20/33 (61%)	Sensitivity data not presented by tumor stage; 59% of cancers studied were Duke's A/B, 41% C/D; all adenomas were LGD	Sensitivity data not presented by tumor location; lesions studied were 50% in proximal colon, 50% in distal	26/28 (93%)

*MSI refers to multiple microsatellite instability markers, including noninherited Bat-26 deletion and others.
†AJCC TNM classification or Duke's staging.
‡Advanced adenoma more than 1 cm, including those with high-grade dysplasia (HGD) and those with low-grade dysplasia (LGD).
§"Proximal" refers to lesions proximal to the splenic flexure.

Fecal DNA versus Fecal Occult Blood for Colorectal-Cancer Screening in an Average-Risk Population

Thomas F. Imperiale, M.D., David F. Ransohoff, M.D., Steven H. Itzkowitz, M.D., Barry A. Turnbull, Ph.D., Michael E. Ross, M.D., for the Colorectal Cancer Study Group

NEJM 2004; 351:2704-2714

Imperiale et al

- Compared DNA test to Hemoccult at 81 sites using average risk people aged 50+
- Subjects submitted one stool specimen for DNA analysis and did standard Hemoccult II test
- Then underwent screening colonoscopy

Imperiale et al. - Results

Most Advanced Finding	DNA Panel (%)	Hemoccult (%)
Adenocarcinoma	16/31 = 52	4/31 = 13
High grade dysplasia	13/40 = 33	6/40 = 15
Adeno + HGD	29/71 = 41	10/71 = 14
Villous adenoma	24/133 = 18	13/133= 10

Imperiale et al. - Conclusions

- Majority of neoplastic lesions identified by colonoscopy were not detected by either test
- Fecal DNA detected a greater proportion of important colorectal neoplasia than Hemoccult II

What have we learned from studies of Canadians? A study by Cotterchio et al. 2005

- Population based case-control study in Ontario
- Incident CRC cases, aged 20 – 74, from Ontario Familial Colorectal Cancer Registry (OFCCR)
- Controls randomly selected from OFCCR population and frequency matched to incident cases
- 971 cases and 1944 controls – about half women
- Significantly more cases than controls had a first degree relative with CRC, BMI >25, ate red meat. Fewer cases than controls used supplemental calcium, and oral contraceptives

What did they find regarding prior screening?

Test	OR	95% CI
FOBT	**0.76 ***	**(0.59 – 0.97)**
Flex Sig	**0.52**	**(0.34 – 0.80)**
Colonoscopy	**0.69**	**(0.44 – 1.07)**
Either endoscopy	**0.62**	**(0.44 – 0.87)**
First FOBT <age 50	0.77	(0.56 – 1.06)
First FOBT >age 50	0.91	(0.64 – 1.28)
First FS <age 50	0.72	(0.52 – 1.01)
First FS >age 50	0.54	(0.35 – 0.83)
First CS <age 50	0.96	(0.62 – 1.49)
First CS >age 50	0.68	(0.47 – 1.00)

"similar to result in Minnesota study"

Authors' Conclusions

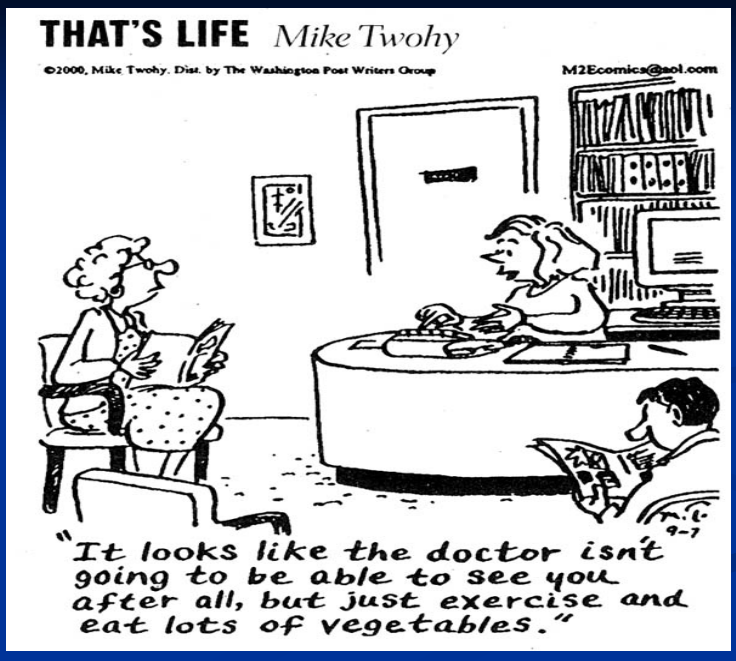
"This study confirmed in a population-based setting that colonic screening is associated with reduced colorectal cancer risk…..These results also demonstrate that the benefits of screening are detectable in the population even with a relatively low prevalence of screening. Thus, a further implication is that efforts must continue to enhance the use of colorectal cancer screening, which will result in further benefits in terms of lives saved and colorectal cancer cases prevented."

What might new recommendations include

- Fecal occult blood tests (FOBT)
  - *>guaiac (SENSA)*
  - *>immunochemical*
- Colonoscopy
- Flexible sigmoidoscopy with and without FOBT
- CT colonography
- Double contrast barium enema (DCBE)

Current Status of CRC Screening in the U.S.

- Screening for colorectal cancer has been shown to reduce deaths (early detection) and prevent disease (removing polyps)
- Leading organizations recommend average risk individuals begin screening at age 50
- Despite good evidence of benefit and supporting policy, screening rates are low. They are lower for people without insurance than for people with insurance



Thank you

Rollins School of Public Health
Emory University