Colorectal Cancer Screening with Stool Tests

Assessing the Quality of Evidence for Efficacy

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Objectives

Identify the available stool based screening tests for colorectal cancer (CRC) in the U.S.

Present the evidence for these tests' ability to detect CRC and advanced polyps

Present the evidence for these tests' effectiveness in reducing incidence and mortality from CRC

Stimulate discussion on how best to prove efficacy of CRC screening tests for guideline makers

Lecture Outline

The available tests

The levels of evidence

The levels of evidence for the available tests

The need for further study of the stool tests

The elephant in the U.S. screening room

Conclusions

The Available Stool Tests

The Guaiac Fecal Occult Blood Test (GT)

- Standard
- High Sensitivity

The Fecal Immunochemical Test (FIT)

The Stool DNA Test (sDNA)

The Levels of Evidence

Level 1

- Evidence from one or more controlled trials

Level 2

- Evidence from cohort or case–control studies

Level 3

- Evidence from diagnostic accuracy studies or case series.

Pignone M, Rich M, Teutsch MN, Berg AO, Lohr KN, Ann Intern Med. 2002;137:132-141.

Guaiac FOBT: Evidence for Efficacy Evidence Level 1

	Mortality Reduction (%)
Minnesota Study	33
Funen Study	18
Nottingham Study	14

Mandel JS, Bond JH, Church TR, et al. N Engl J Med 1993 May 13; 328(19):1365-71.
Kronborg O, Fenger C, Olsen J, et al. Lancet 1996 Nov 30; 348:1467-71.
Hardcastle JD, Chamberlain JO, Robinson MH, et al. Lancet 1996 Nov 30; 348:1472-7.
Mandel JS, Church TR, Bond JH, et al. N Engl J Med 2000; 343:1603-1607.

Guaiac Testing and the Digital Rectal Exam (DRE)

- *DRE itself is not associated with a reduction in mortality in distal rectal cancer*
- *DRE with FOBT cannot be recommended as a colon cancer screening test.*
- *Guidelines do not endorse DRE alone or FOBT testing of a specimen obtained by this method. (The Multisociety GI Task Force, the American Cancer Society, and the National Comprehensive Cancer Network (NCCN) Colorectal Cancer Screening)*

Collins JF, Lieberman DA, Durbin TE, Weiss DG, Ann Intern Med. 2005;142:81-85.

“If new screening tests are truly more accurate than Hemoccult II, their effectiveness need not be confirmed by randomized controlled trials because Hemoccult II’s ability to save lives from colorectal cancer has already been shown.”

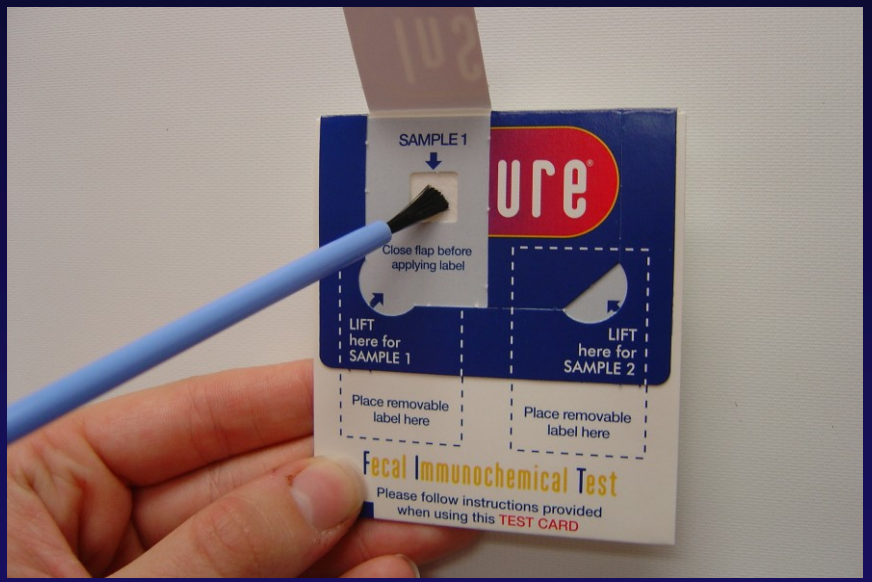
Fletcher RH. Commentary.
ACP Journal Club 1996
May-June;124(3):74

The Fecal Immunochemical Test (FIT)

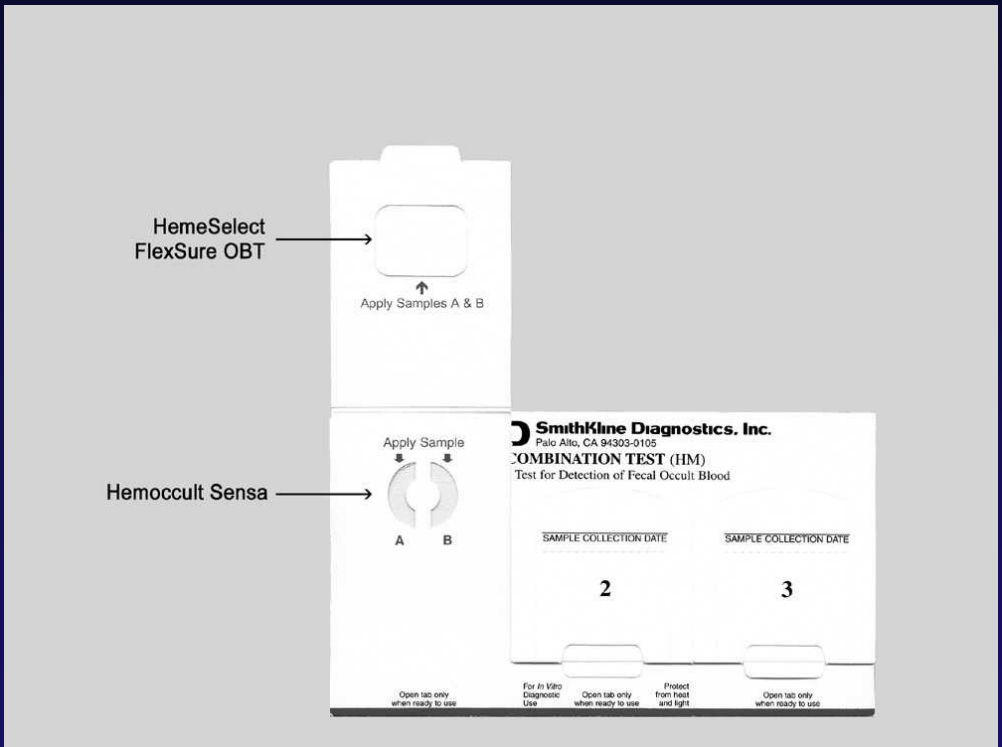
- Uses antibodies specific for human globin
- Specific for colonic bleeding
- Not affected by diet or medications
- FDA approved
- Authorized reimbursement by CMS for use in Medicare patients
- Some allow for quantification of fecal hemoglobin
- Can be read and developed by technicians or by automated readers and developers

FIT: Sample Collection

- Brush over surface of stool while immersed
- Lift the flap and dab card with specimen
- Close flap & seal with barcode
- Repeat with next stool
- Mail in reply-paid envelope to lab for development



Comparison Test Card
FOBT/FIT



FIT Performance Characteristics

Table 2. Performance Characteristics of Fecal Occult-Blood Tests.

Test and Finding*	Sensitivity	Specificity	Positive Predictive Value
	percent (95% confidence interval)		
Hemoccult II			
Carcinoma	37.1 (19.7–54.6)	97.7 (97.3–98.0)	6.6 (3.7–11.2)
Polyp ≥1 cm	30.8 (21.6–40.1)	98.1 (97.7–98.4)	16.7 (11.9–22.8)
Combined	32.4 (24.3–40.4)	98.1 (97.7–98.4)	23.2 (17.7–29.9)
Hemoccult II Sensa			
Carcinoma	79.4 (64.3–94.5)	86.7 (85.9–87.4)	2.5 (1.7–3.7)
Polyp ≥1 cm	68.6 (59.2–77.9)	87.5 (86.7–88.2)	6.7 (5.3–8.4)
Combined	71.2 (63.3–79.1)	87.5 (86.7–88.2)	9.2 (7.6–11.2)
HemeSelect			
Carcinoma	68.8 (51.1–86.4)	94.4 (93.8–94.9)	5.0 (3.2–7.6)
Polyp ≥1 cm	66.7 (57.0–76.3)	95.2 (94.7–95.7)	15.5 (12.3–19.3)
Combined	67.2 (58.8–75.5)	95.2 (94.7–95.7)	20.5 (16.8–24.6)
Combination			
Carcinoma	65.6 (47.6–83.6)	97.3 (96.9–97.6)	9.0 (5.8–13.6)
Polyp ≥1 cm	50.0 (39.8–60.2)	97.9 (97.6–98.2)	21.9 (16.9–27.9)
Combined	53.7 (44.9–62.5)	97.9 (97.6–98.2)	30.9 (25.1–37.3)

*The calculations for polyps did not include patients with carcinoma.

Allison JE, Tekawa IS, Ransom LJ, Adrain AL. N Engl J Med 1996; 334:155-9

FIT Performance Characteristics

Table 3. Fecal occult blood test (Hemoccult Sensa), fecal immunochemical test (FlexSure OBT), and combination test performance characteristics in a population at average risk for colorectal cancer*

Finding per test	No of persons screened	No of neoplasms detected	Sensitivity		Specificity		Positive predictive value		Likelihood ratio (+)	
			No./ total	% (95% CI)	No./ total	% (95% CI)	No./ total	% (95% CI)	Ratio	(95% CI)
Distal cancer										
Hemoccult Sensa	5799	14	9/14	64.3 (35.6 to 86.0)	5210/5785	90.1 (89.3 to 90.8)	9/584	1.5 (0.8 to 3.0)	6.5	(4.3 to 9.6)
FlexSure OBT	5356	11	9/11	81.8 (47.8 to 96.8)	5181/5345	96.9 (96.4 to 97.4)	9/173	5.2 (2.6 to 10.0)	26.7	(19.4 to 36.6)
Hemoccult Sensa + FlexSure OBT	5819	14	9/14	64.3 (35.6 to 86.0)	5693/5805	98.1 (97.7 to 98.4)	9/121	7.4 (3.7 to 14.0)	33.3	(21.6 to 51.3)
Distal adenomas ≥1 cm										
Hemoccult Sensa	5799	126	52/126	41.3 (32.7 to 50.4)	5141/5673	90.6 (89.8 to 91.4)	52/584	8.9 (6.8 to 11.6)	4.4	(3.5 to 5.5)
FlexSure OBT	5356	112	33/112	29.5 (21.4 to 38.9)	5104/5244	97.3 (96.8 to 97.7)	33/173	19.1 (13.7 to 25.9)	11.0	(7.9 to 15.3)
Hemoccult Sensa + FlexSure OBT	5819	127	29/127	22.8 (16.1 to 31.3)	5600/5692	98.4 (98.0 to 98.7)	29/121	24.0 (16.9 to 32.7)	14.1	(9.7 to 20.6)
Distal advanced neoplasms										
Hemoccult Sensa	5799	137	59/137	43.1 (34.7 to 51.8)	5137/5662	90.7 (89.9 to 91.5)	59/584	10.1 (7.8 to 12.9)	4.6	(3.8 to 5.7)
FlexSure OBT	5356	121	40/121	33.1 (24.9 to 42.3)	5102/5235	97.5 (97.0 to 97.9)	40/173	23.1 (17.2 to 30.3)	13.0	(9.6 to 17.6)
Hemoccult Sensa + FlexSure OBT	5819	138	36/138	26.1 (19.2 to 34.4)	5596/5681	98.5 (98.1 to 98.8)	36/121	29.8 (22.0 to 38.9)	17.4	(12.3 to 24.8)

* Likelihood ratio (+) = sensitivity/(1 − specificity); CI = confidence interval.

Allison JE, Sakoda LC, Levin TR, et al. J Natl Cancer Inst 2007;99: 1-9.

FIT Performance Characteristics

Table 2. Results of Immunochemical FOBT and Colonoscopic Findings

	No neoplasia	Neoplasia	Advanced neoplasia						
			Total	Adenoma ≥10 mm*	High-grade dysplasia	Invasive cancer			
						Total	Dukes' stage A	Dukes' stage B	Dukes stages C or D
Negative test (%) (n = 20,574)	16,698 (81.2)	3876 (18.8)	530 (26)	423 (2.1)	80 (0.4)	27 (0.1)	17	3	5
Positive test (%) (n = 1231)	782 (63.5)	449 (36.5)	197 (16.0)	106 (8.6)	39 (3.2)	52 (4.2)	19	7	18
Sensitivity (%) (95% CI)		10.4 (9.5-11.3)	27.1 (23.9-30.3)	**20.0** (16.6-23.4)	**32.7** (24.3-41.2)	**65.8** (55.4-76.3)	52.8 (36.5-69.1)	70.0 (41.6-98.4)	78.3 (61.4-95.1)
Specificity (%) (95% CI)		**95.5** (95.2-95.8)	**95.1** (94.8-95.4)			94.6 (94.3-94.9)			

CI, confidence Interval.
*Except adenomas with high-grade dysplasia

Morikawa T, Katao J, Yamafi Y et al Gastroenterology 2005;125:422-428

Summary - FIT Superior to GT Evidence Level 3

- Performance/Acceptance advantages:
  - Better sensitivity than standard GT
  - Better specificity than sensitive GT
  - Selective for colorectal bleeding
  - No need for diet or drug restrictions
- Processing advantages:
  - Quantifiable
  - Automatable
  - Computer generated distribution, reporting, reminders

Mirror Mirror on the wall
Which is the FIT - Test of them all?

InSure

Hemoccult ICT

Magstream 1000/Hem SP

immoCARE

MonoHaem

QuickVue iFOB

FIT – Outstanding Issues

- *Are quantitative FITs an advantage over qualitative FITS?*
- *At what level of Hemoglobin detection should FITs be set?*
- *Which sampling technique is most acceptable to patients*
- *How many stool specimens should be tested for optimal sensitivity and specificity?*
- *Are FITs best evaluated in the laboratory or the physician's office?*
- *Are FITs best interpreted by technicians or automated technology*

Stool-based DNA Assays

What is it?

- *Relies on DNA markers exfoliated from the neoplastic colonic epithelial cells*
- *PreGen-Plus™', is comprised of 23 molecular markers that are known to be associated with colorectal cancer.*
- *Potential for screening for these different mutations using PCR amplification technologies*

Fecal DNA Tests
The Thought Leaders Speak

"Stool screening has historically relied on detection of occult blood, which has been proven to be an inherently insensitive and nonspecific marker for screen relevant neoplasia."

Osborn NK and Ahlquist DH Gastroenterology 2005:128:192-206

Performance Characteristics Multi target DNA stool tests

Table 4. Colorectal Neoplasia Detection by Multi target DNA Testing in Stool

Reference	Test sensitivity, % (n)			Test specificity, % (n)
	Marker panel	Cancer	Adenomas	
Pre-Gene-Plus				
Ahlquist et al 2000[61]	APC, *K-ras*, p53; MSI; Long DNA	91 (20/22)	82 (9/11)	93 (26/28)
Tagore et al 2000[92]	APC, *K-ras*, p53, MSI; Long DNA	63 (33/52)	57 (16/28)	98.2 (111/113)
Syngal et al 2002[93,105] and 2003[104]	APC, *K-ras*, p53; MSI; Long DNA	62 (40/65)	27 (6/22)	
Brand et al 2002[124]	APC, *K-ras*, p53; MSI; Long DNA	69 (11/16)		
Calistri et al 2003[73]	APC, *K-ras*, p53; MSI; Long DNA	62 (33/53)		97 (37/38)
Other Panels				
Dong et al 2001[109]	p53, *K-ras*, MSI	71 (36/51)		
Rengucci et al 2001[110]	p53, *K-ras*; MSI	67 (31/46)		100 (18/18)
Koshiji et al 2002[114]	LOH; MSI	97 (29/30)		100 (30/30)

Stool DNA Test: Performance Characteristics

DNA Test	# tested/ evaluated	Sensitivity CA (%) (95% CI)	Specificity CA (%) (95% CI)	Sensitivity Advanced Adenoma (95%CI)	Specificity Advanced Adenoma (95%CI)
PreGenPlus™ (Prototype)	61/61	91 (71-99)	93 (76-99)	82 (48-98)	93 (76-99)
PreGenPlus™ (V1)	4404/2507	51.6 (34.8-68.0)		15.1 (12.0-19.0)	94.4 (93.1-95.5)
PreGenPlus™ (V1)	3764	25		20	
PreGenPlus™ (V2)	162	87.5	82		

Ahlquist DA, et al. Gastroenterology 2000; 119:1219-1227.
Imperiale TF, Ransohoff DF, Itzkowitz SH, et al N Engl J Med. 2004 Dec 23;351(26):2704-14..
Ahlquist DA, Sargent DJ, Levin TR, Rex DK, et al Gastroenterology 2005:128, No. 4, Supply 2 A63.
Itzkowitz SH, Jandorf L, Brand R, et al Gastroenterology and Hepatology 2007 5:111-117.

Stool DNA Tests The Evidence Speaks

Stool DNA Test Versus FIT

Stool DNA Test	Sensitivity CRCA (%)	Sensitivity Polyp≥1cm (%)	Specificity CRCA (%)	Specificity Polyp≥1cm (%)
Pre Gen V1 (NEJM)	52	15		94
Pre Gen V1 (Mayo)	25	20		
Magstream	66	20	95	95
Hemoccult ICT	82*	30	97	97

** Left sided neoplasms.*

sDNA Test Outstanding Issues

- FDA approval
- Demonstration of cost effectiveness by AHRQ analysis
- Final configuration of the test to be marketed
- Inconsistency in performance of PreGen+ (V1) demonstrated in large multicenter studies
- Do updated versions of the test need to be tested in large average risk populations?
- Suggested intervals between tests

Conclusions

- FITs overcome most of the disadvantages presented by GT
- Based on performance characteristics estimated in large populations of average risk patients, FIT should replace GT in screening for CRC
- More studies are necessary to determine which FIT is best

Conclusions

- The stool DNA test is a promising technology but, based on evidence from screening studies in large average risk populations, it does not appear that in its present form it is an improvement over the less costly and more easily performed FIT

Conclusions

- Evidence of stool test efficacy for mortality reduction or detection of advanced neoplasia does not have to come from randomized controlled trials if the newer tests can be shown to have superior performance characteristics when compared to the standard GT.
- Performance characteristics of stool tests are most accurately determined when a gold standard structural test is used to evaluate the test negative subjects

“No test is perfect but any is better than none”

Allison JE Evidence Based Gastroenterology 2005;6:15-16

Issues for Discussion

- The elephant in the screening room
- Funding for studies of screening tests other than colonoscopy
- Guidelines free of professional and industry bias
- Screening networks – national, international
- Screening “Centers of Excellence”

Optical Colonoscopy

Cecal Stampede:
The Headlong Rush for Screening Colonoscopy

Lawson MJ, Tobi M Dig Dis Sci 2008;53(4):871-4

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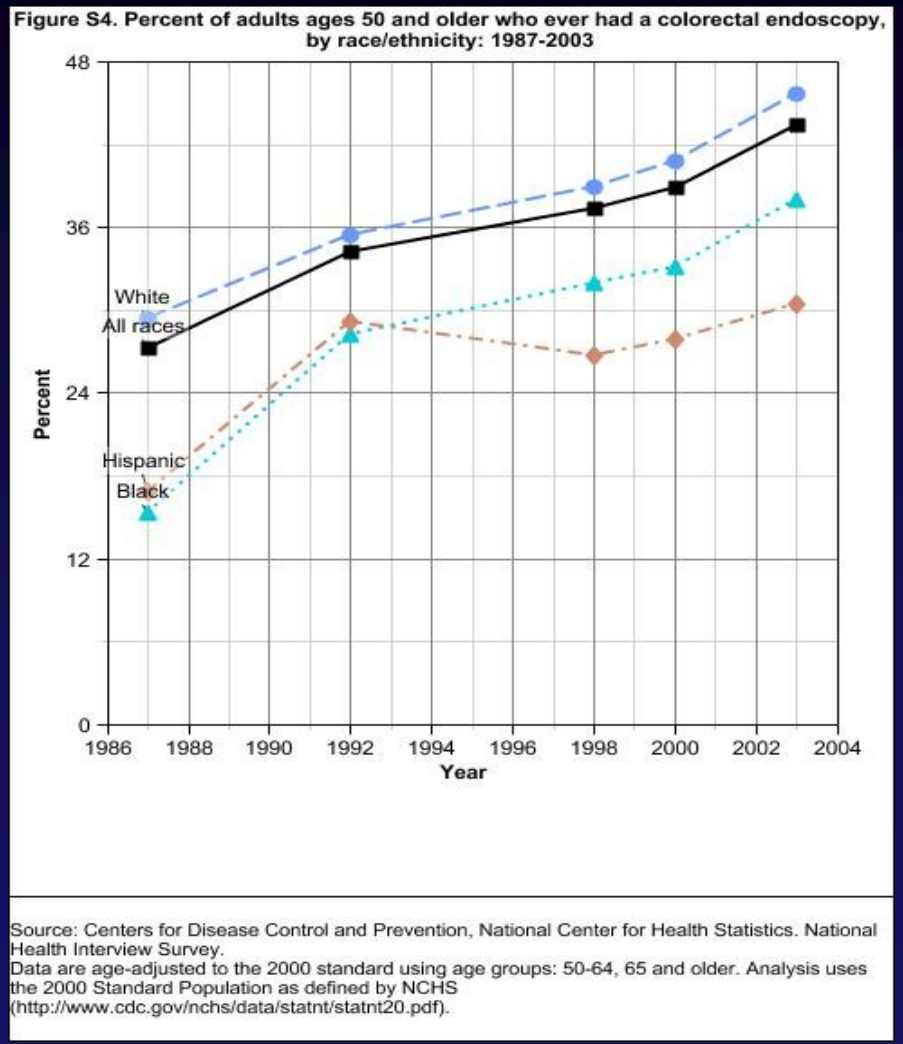
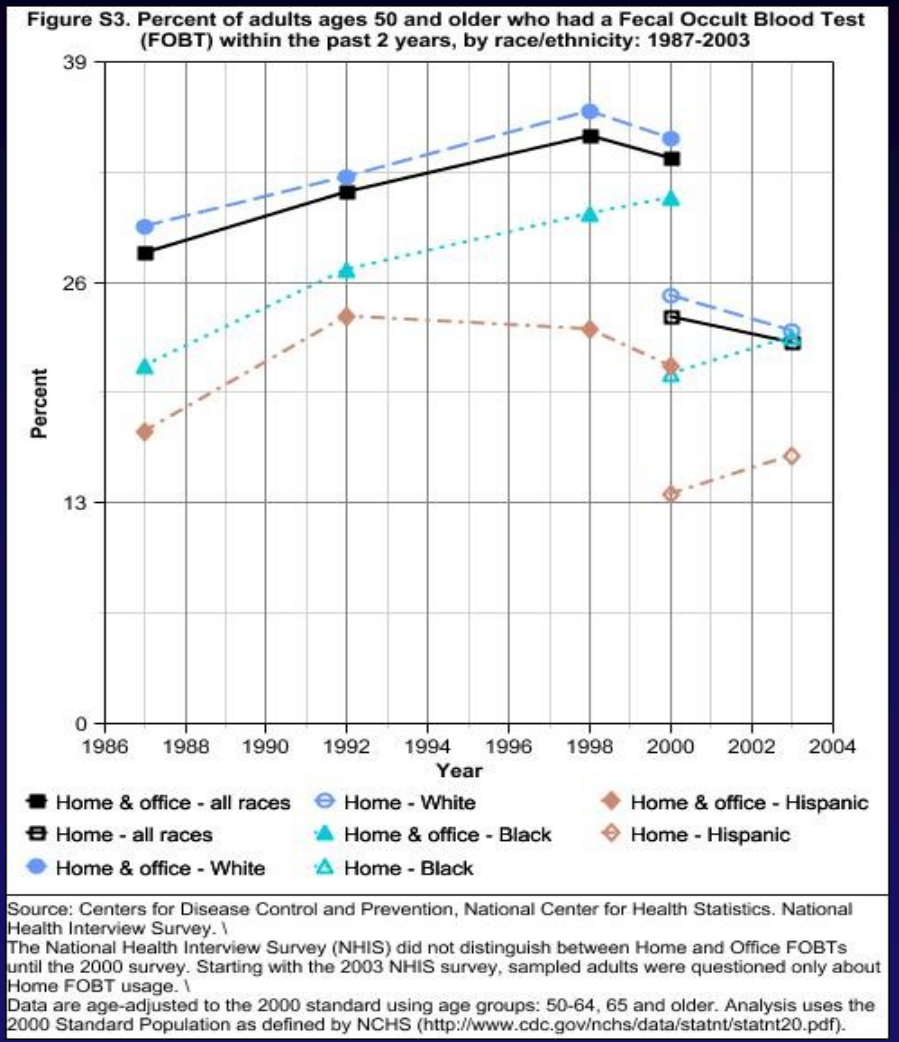
Screening Rate Endoscopy



Screening Rate for FOBT



ACS/USMSTF and ACR Guidelines
Precautions Re Menu of Options

If fecal tests are used the “opportunity for prevention is both limited and incidental and not the primary goal of CRC screening with these tests.”

“It is the strong opinion of this expert panel that colon cancer prevention should be the primary goal of CRC screening and that providers and patients should understand that noninvasive tests are less likely to prevent cancer compared with the invasive tests.”