


OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: J. Allison



**World Organisation of
Digestive Endoscopy**

Colorectal Cancer Screening Committee Meeting


**Comparison of Test Performance
A Tale of Three Studies**

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Outline


- **Comparative studies**
 - The important components
- **Examples of comparative studies**
 - FIT versus gFOBT
 - The good, The bad, The ugly
 - DNA stool test versus gFOBT
 - The good, The bad, The ugly
- **Questions for the future**



Comparative Studies of Screening Tests

Important Components

- **Population**
 - Number – should be large (N = 2000-10000)
 - Character – multiethnic, gender equal and average risk ideal
- **Comparator Screening test characteristics**
 - Patient friendly
 - No dietary restriction
 - Small number of samples required
 - Minimum amount of stool handling required
- **Screening test standard**
 - A test that has been evaluated in randomized controlled studies
- **Gold standard evaluation of the negatives**
 - Structural examination preferably optical colonoscopy



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Study 1 The Good, the Bad and the Ugly

- **The Good**
 - Large numbers in average risk multiethnic population
 - Unique comparator test card
 - Ability to test same patient with 4 different stool screening tests
- **The Bad**
 - Dietary restriction required
 - Test negatives not evaluated with gold standard structural exam
- **The Ugly**
 - Not used for making guideline recommendations



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	Dukes' stages		
								stage A	stage B	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 = 1233)	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, Yamaji Y et al Gastroenterology 2005;125:422-428



FIT Performance Characteristics

Table 3. Fecal occult blood test (Hemoccult Senses), 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 assessed	No. of neoplasms detected	Sensitivity		Specificity		Positive predictive value		Likelihood ratio (L)	
			No./total	% (95% CI)	No./total	% (95% CI)	No./total	% (95% CI)	Diagn.	Denom.
Overall case rate										
Hemoccult Senses	9799	34	34	34.3 (23.0 to 45.6)	32,127,119	99.9 (99.9 to 100.0)	9994	3.0 (2.6 to 3.4)	0.9	98.0 to 99.0
FlexSure OBT	5266	11	11	91.8 (67.9 to 95.8)	51,819,345	99.9 (99.9 to 100.0)	6179	5.2 (2.6 to 10.2)	28.7	10.4 to 34.8
Maximum Test Score = 2 FlexSure OBT	5266	14	14	64.3 (45.9 to 82.7)	52,022,842	99.9 (99.9 to 100.0)	6191	7.4 (5.7 to 10.0)	22.9	10.4 to 41.9
Overall adenoma rate										
Hemoccult Senses	5700	130	130	52.9 (41.3 to 64.5)	51,441,673	99.9 (99.9 to 100.0)	51,634	8.8 (8.0 to 11.0)	4.4	3.5 to 5.3
FlexSure OBT	5266	112	112	33.9 (24.4 to 43.4)	51,849,244	97.3 (96.9 to 97.7)	33,773	19.1 (17.4 to 20.9)	11.0	47.9 to 15.3
Maximum Test Score = 2 FlexSure OBT	5266	127	127	29.1 (21.1 to 37.1)	50,809,492	99.4 (99.3 to 99.5)	29,671	24.8 (19.9 to 32.7)	14.1	6.7 to 28.8
Overall adenoma rate										
Hemoccult Senses	9799	137	137	62.3 (54.1 to 70.5)	51,371,941	99.7 (99.7 to 99.8)	51,994	10.1 (7.0 to 13.3)	4.6	3.0 to 6.7
FlexSure OBT	5266	121	121	40.1 (34.9 to 45.3)	51,802,239	97.5 (97.0 to 97.9)	40,779	22.1 (17.2 to 28.2)	13.0	6.6 to 17.8
Maximum Test Score = 2 FlexSure OBT	5266	139	139	26.1 (19.2 to 34.0)	50,904,841	99.8 (99.8 to 99.9)	36,731	20.8 (12.6 to 34.0)	17.4	11.3 to 24.8

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




Study 2 **The Good, the Bad and the Ugly**

- **The Good**
 - Large numbers in average risk multiethnic population
 - Unique comparator test card
 - Ability to test same patient with 4 different stool screening tests
 - Dietary restriction (except for no vitamin C) not required
 - Enough important components for use in guidelines
- **The Bad**
 - Test negatives not evaluated with colonoscopy
- **The Ugly**
 - Conclusions had to be limited to left sided advanced neoplasms



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

- 
- InSure
 - Hemoccult ICT
 - Magstream 1000/Hem SP
 - immoCARE
 - Polymedco
 - QuickVue iFOB

FIT – Outstanding Issues

- Which of the many FITs on the market is best?
- Do quantitative FITs offer 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 developed and interpreted by technicians or by automated technology



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	52	15		94
Pre Gen V1	25	20		
Magstream	66	20	95	95
Hemoccult ICT	82*	30	97	97

* Left sided neoplasms.



Study 3 The Good, the Bad and the Ugly

- **The Good**
 - Large numbers in average risk multiethnic population
 - No dietary restriction required
 - Test negatives evaluated with colonoscopy
- **The Bad**
 - Only a proportion of test negatives evaluated with colonoscopy
 - Large numbers of contributing centers with varying oversight of quality control in the development of the comparator gFOBT
- **The Ugly**
 - Results did not confirm earlier studies of small populations with known neoplasms
 - Performance characteristics for gFOBT the lowest reported in the literature



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 with gold standard colonoscopy evaluation of the negatives?
- Suggested intervals between tests



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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”