


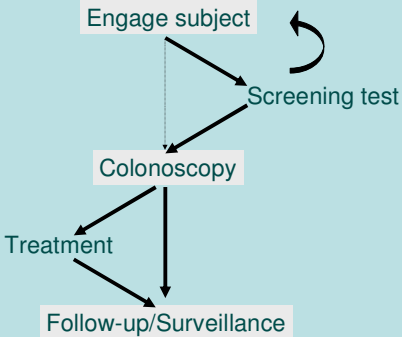


What endpoints matter when evaluating new screening tests?

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Simple tests select for colonoscopy



WHO requirements of a screening test

Given that CRC is an important problem:

- Be shown in the absence of bias to reduce mortality (and incidence)
- Be cost-effective (and also feasible)
- Be acceptable to the people being targeted
- (Benefit outweighs the down-side)



OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 19, DDW Washington, 2007


Presenter: G. Young

Key endpoints - Status of GFOBT*

1. Reduce mortality	yes
2. Reduce incidence	yes
3. Cost-effective	yes
4. Acceptable	yes

Inadequacies:


- Inflexible qualitative endpoint
- Lack sensitivity for adenomas

*GFOBT – guaiac FOBT 

Issue for consideration


How far do we need to go in evaluating new tests?

- Are there surrogate markers that reflect the key endpoints?
- What study design and context allows us to efficiently evaluate multiple tests?
- Given that GFOBT are proven, are these the appropriate comparator?



1. Mortality reduction

- Depends on detection of cancer in a curable stage (UICC stages 0-II)
- Thus better detection of cancer equates to a better impact on mortality
 - Reflected in a higher positivity rate in those known to have cancer
 - Paired testing in cases with cancer provides great power to detect a difference in sensitivity



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Does context matter? - 1

- Tests often initially compared in cohorts undergoing diagnostic colonoscopy
 - Will include stage III and IV cancers
 - Feasible with n=25
- There is a preference for comparative evaluation in screen-detected cancers (asymptomatic, predominantly Stage 0-II)
 - Requires n=2,-5,000 depending on cancer prevalence!



FIT Identify more Cancers

		Hemoccult SENSА (GFOBT)		
		Positive	Negative	
InSure (FIT)	Positive	13	8	21 (88%)
	Negative	0	3	3
		13 (54%)	11	n=24

Difference 33%, CI 11-55%

Smith et al Cancer. 2006;107:2152-2159



Does context matter? - 2

- There is evidence that comparative performance in a diagnostic cohort holds true in a screening cohort
 - Smith et al Cancer. 2006;107:2152-2159
- Actual estimates of sensitivity will not necessarily, however, be accurate when a diagnostic cohort is included.



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2. Incidence reduction

- Depends on detection of adenomas, especially those associated with a greater likelihood to progress
- Thus better detection of advanced/significant adenomas equates to a better impact on incidence
 - Reflected in a better positivity rate in those known to have significant adenomas
 - Paired testing in cases provides great power to detect a difference in sensitivity
- Can only be determined in the screening context
 - E.g. Smith et al Cancer, 2006;107:2152-2159



3. Cost-effectiveness

- Complex issue more important in public health than case-finding environment
- Cost-effectiveness studies show that the number of colonoscopies required is the major determinant of the cost of a screening program.
- Thus, test-positivity rate (TPR) is a surrogate for cost.
- Many funders want to control TPR.



Contexts for studying TPR

- Healthy people unlikely to have cancer or asymptomatic people with a normal colon
 - Estimate of false-positive rate (FPR);
 - $1 - \text{FPR} = \text{specificity}$
- True screening population where all expected pathologies will be found
 - Estimates colonoscopy rate in target population
- Undertake paired testing vs proven test
 - $N=500$ gives power to detect a 2% difference



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4. Acceptability


- Without participation, detection is impossible
- Acceptability is reflected in participation rates

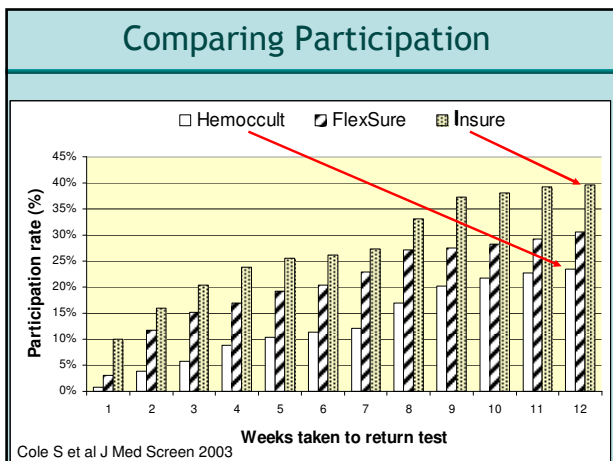
Test	Participation rate	Sensitivity	Cancer yield in population
A	50%	50%	25%
B	25%	95%	25%



Context for studying participation


- Use a typical target population
- Randomly select separate cohorts for each test
- Offer test in the usual manner
- Note: intense advocacy masks differences
- N=600 gives good power to detect a 7.5% difference






Comparing performance

- True sensitivity, specificity, PPV and NPV are largely theoretical in the screening context and are very hard to measure.
- Better to study the surrogate measures for important screening endpoints:
 - Relative detection rate (cancers, adenomas)
 - Positivity rate, and
 - Participation rate
- These accurately reflect the key measures in screening programs
- Improvement in any one is worthwhile



What about incremental benefit?

- For example, if a new test has a better detection rate, is an increase in positivity rate necessary to achieve this worthwhile?




Kaiser study, 1996

Parameter	HemSel	Hemoccult	HOSENSA
Sensitivity cancer	69% ^a	37%	79% ^a
Positive tests	5.9%	2.5%	13.6%
PPV	5%	6.6%	2.5%
Colonoscopies per extra cancer	1.27	-	2.55

^aSignificantly different from Hemoccult

Heme Select ("HemSel") is an FIT; no longer available.
Allison et al, NEJM 1996; (n=7493 to 8065)



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Conclusion

- To evaluate new tests, we do not need RCTs with mortality as the end-point. Surrogate endpoints will give the necessary information quickly in properly designed and conducted studies.
- The comparator should be Hemocult
- However, where the down-side of testing is not clear, e.g. potentially fatal complications, large RCTs with collection of all outcomes will be required.



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