Decision Analysis of Colorectal Cancer Screening Tests by Age to Begin, Age to End, and Screening Intervals:

Report to the United States Preventive Services Task Force from the Cancer Intervention and Surveillance Modeling Network (CISNET)

Institute of Medicine, Washington DC
February 25 , 2008

CANCER INTERVENTION AND SURVEILLANCE MODELING NETWORK

MISCAN

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Outline

Questions to CRC CISNET from USPSTF on CRC screening

Microsimulation modeling

- MISCAN
- SimCRC

Methodology

Results

Discussion

Costs

Questions addressed by CISNET for USPSTF 2007

2007 USPSTF addresses colorectal cancer screening recommendations

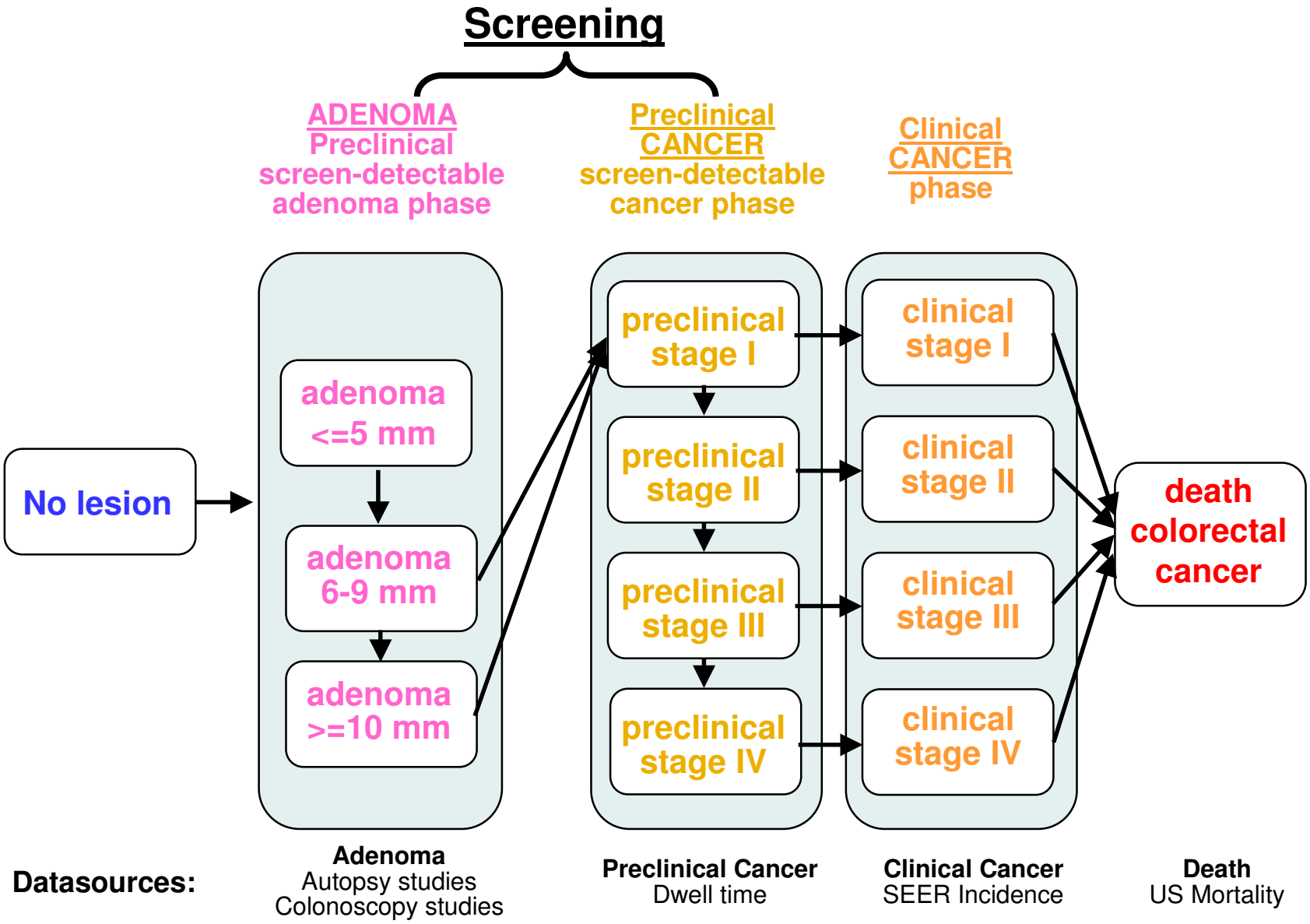
Task Force requested a decision analysis for recommended CRC screening tests for

- age to begin
- age to end
- rescreening interval
- *Should the current recommendations be changed?*

Microsimulation models (MISCAN and SimCRC) of CISNET consortium used for the decision analysis.

NO DECISION ANNOUNCED BY TASK FORCE

Microsimulation Modeling of Adenoma Carcinoma Sequence with Screening Intervention



Model Differences

MISCAN has a shorter dwell time from adenoma to clinically detected cancer *on average* (10 years)

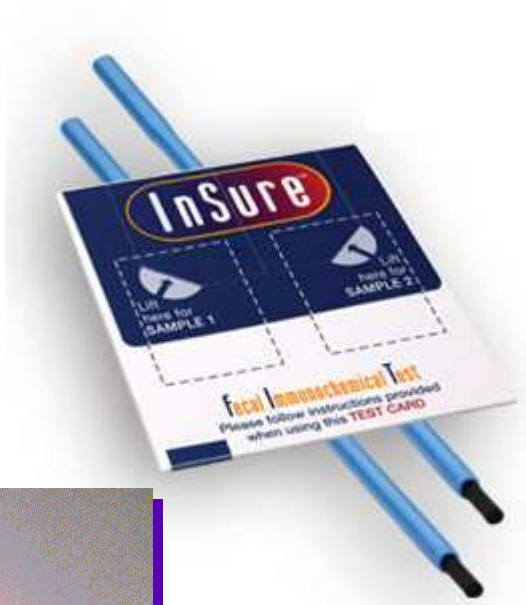
SimCRC has a longer dwell time *on average* (22 years)

Dwell time is an unmeasured 'deep' parameter

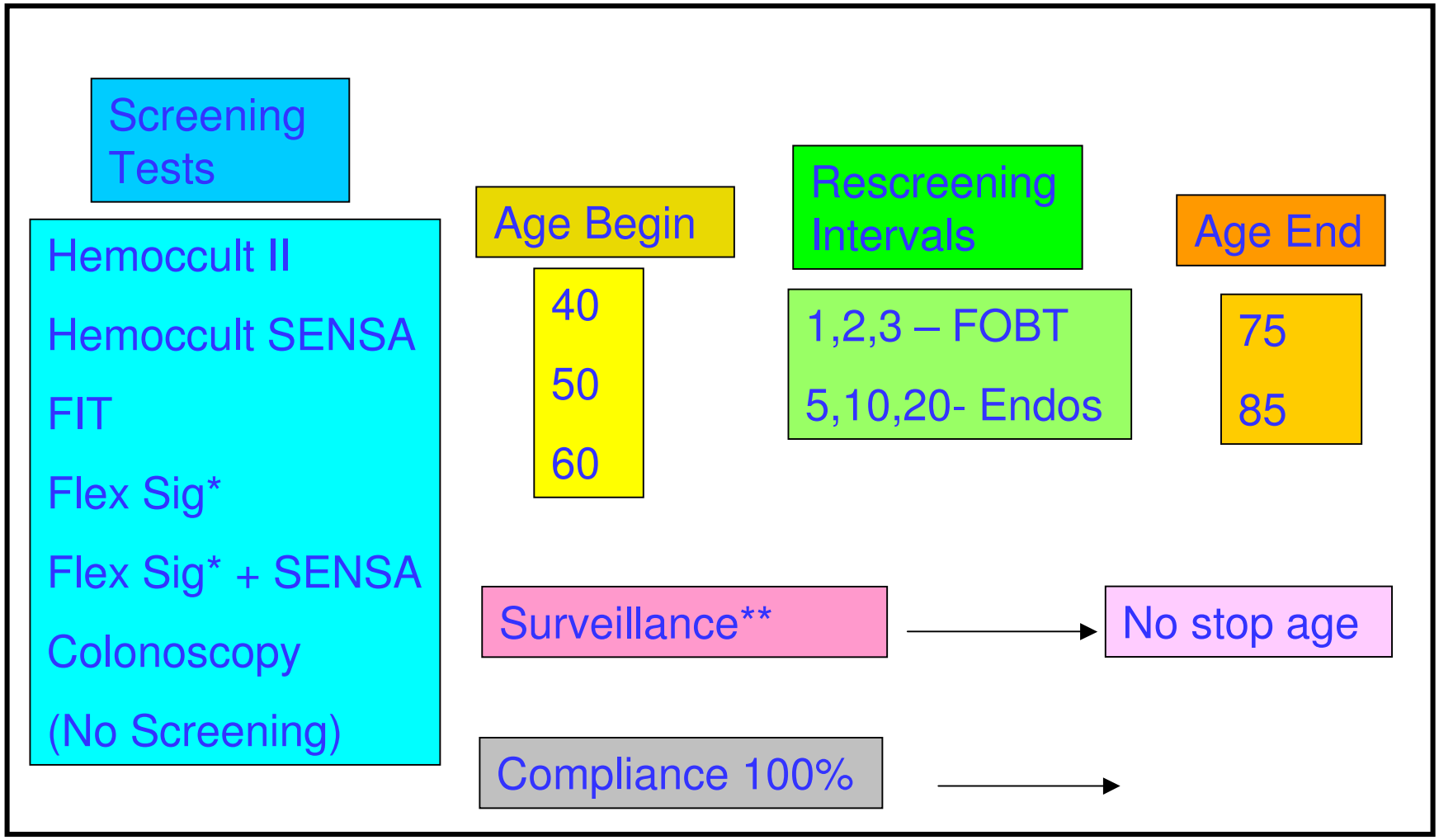
Implications of differences in dwell time to the screening strategies:

- More life years gained from screening for SimCRC
- Additional benefit of increasing screening frequency will be greater for MISCAN

Colorectal Cancer Screening Tests



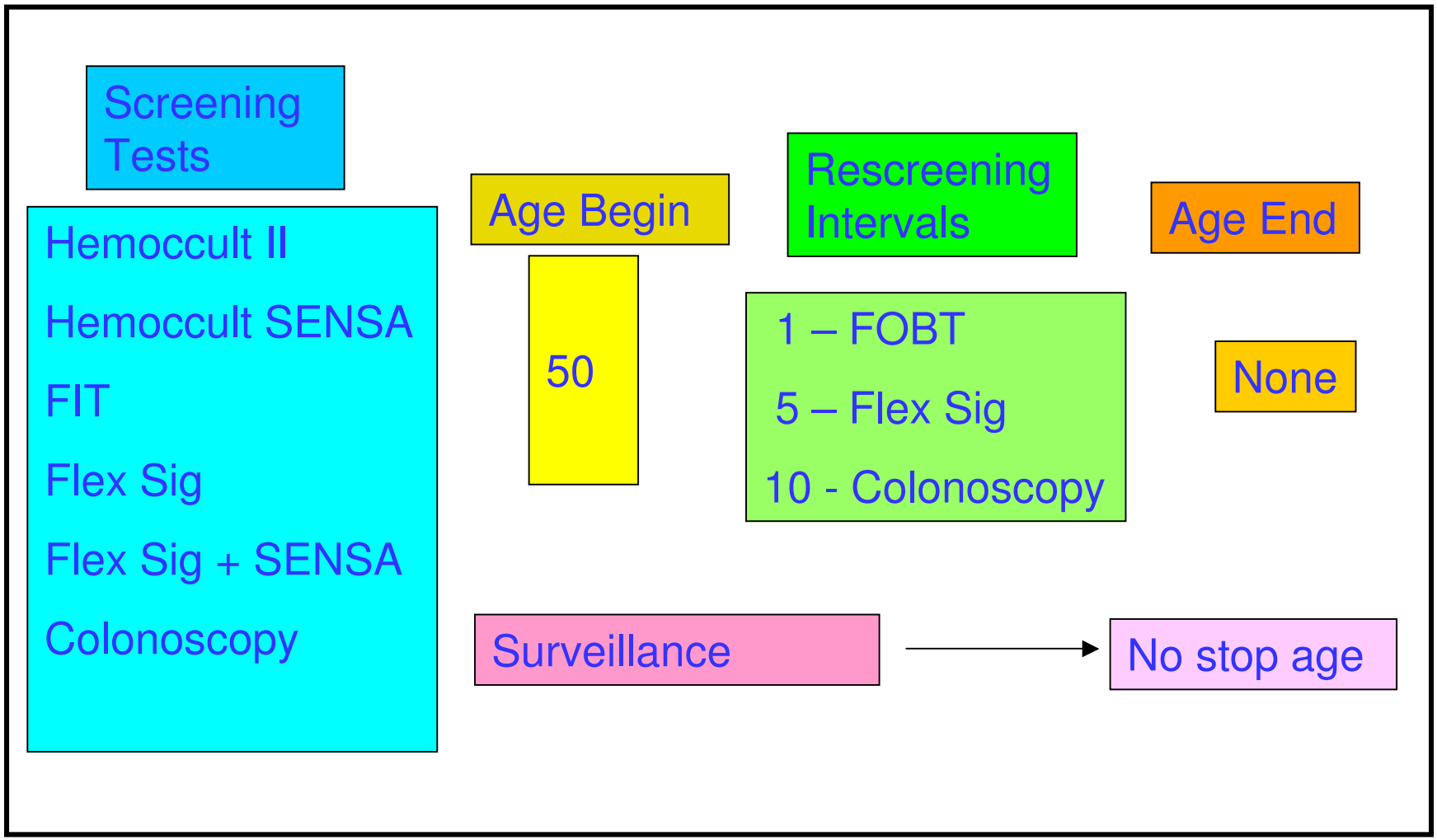
Colorectal Cancer Screening Strategies
Cohort of 40 year olds in 2005



* *With biopsy*

** *3 year for advanced adenomas, 5-10 (5) for non-advanced adenomas*

Colorectal Cancer Screening Strategies
Current Age and Interval Recommendations*



* MultiSociety and ACS

Colorectal Cancer Screening Strategies
Current CMS reimbursement

Screening Tests	CMS reimbursement*
Guaiac FOBT (II or SENSA)	$4.50
Immunochemical FOBT (FIT)	$22.22
Flex Sig	$161/$348
Flex Sig + SENSA	$165/$352
Colonoscopy	$498/$649

*CMS Report 2007

Table 1: Test Characteristics Base Case

Test Characteristics	Hemoccult II	Hemoccult SENSA	FIT	Sigmoido-scopy*	Colonoscopy
Specificity	98%	92.5%	95%	100%	100%
Sensitivity				Se within reach:	
Adenomas ≤0.5	2%	7.5%	5%	75%	75%
0.6-0.9	5%	12%	10%	85%	85%
≥1.0	12%	24%	22%	95%	95%
Cancers	40%	70%	70%	95%	95%
Reach	Whole colorectum	Whole colorectum	Whole colorectum	80% reach sigmoid-descending colon junct (60 to sig-des and 80 splenic)	95% reach cecum

*Sensitivity for CRC for Sigmoidoscopy for whole colon comparable to Evidence Review

Table 1: Test Characteristics

SENSITIVITY ANALYSIS – (*Worst and Best)*

Test Characteristics	Hemoccult II	Hemoccult SENSA	FIT	Sigmoido-scopy	Colonoscopy
Specificity	98% (95-99)	92.5% (90-95)	95% (92.5-98)	100%	100%
<u>Sensitivity</u>				Se within reach:	
Adenomas ≤0.5	2% (1-5)	7.5% (5-10)	5% (2-7.5)	75% (70-79)	75% (70-79)
0.6-0.9	5% (5-14)	12% (10-26)	10% (7.5-24)	85% (80-92)	85% (80-92)
≥1.0	12% (10-28)	24% (16-48)	22% (16-48)	95% (92-99)	95% (92-99)
Cancers	40% (29-50)	70% (50-87)	70% (50-87)	95% (92-99)	95% (92-99)
Reach	Whole colorectum	Whole colorectum	Whole colorectum	80% reach sigmoid-descending colon junct (60 to sig-des and 80 splenic)	95% reach cecum

Outcome Measures

Most effective = Greatest life years gained relative to no screening

Weigh effectiveness *against*
resources required and exposure to risks:
Colonoscopy as resource and risk indicator

- Endoscopy resources
- Perforation risk

Life years gained (LYG) vs
Total colonoscopies in lifetime

(per 1000 persons in population)

.

Effectiveness-Risk Analysis to evaluate 145 strategies

If strategy requires more colonoscopies but has fewer life years gained (LYG) *(ie less effective)* then eliminate.

Of the remaining strategies, derive relative to each other

- Incremental number of colonoscopies = ΔCol
- Incremental LYG = ΔLYG
- Incremental number colonoscopies to gain a life yr = ΔCol/ ΔLYG
- If strategy is less effective with a higher ΔCol/ ΔLYG than another, then this strategy is eliminated due to *extended dominance*

Efficiency frontier – all strategies NOT dominated

Near the efficiency frontier – those strategies that are with 98% of the LYG on the frontier

Comparisons

First compare strategies within a screening test

Efficient frontier derived for each screening test or combination test

ΔCol/ΔLYG – 'Efficiency Ratio'

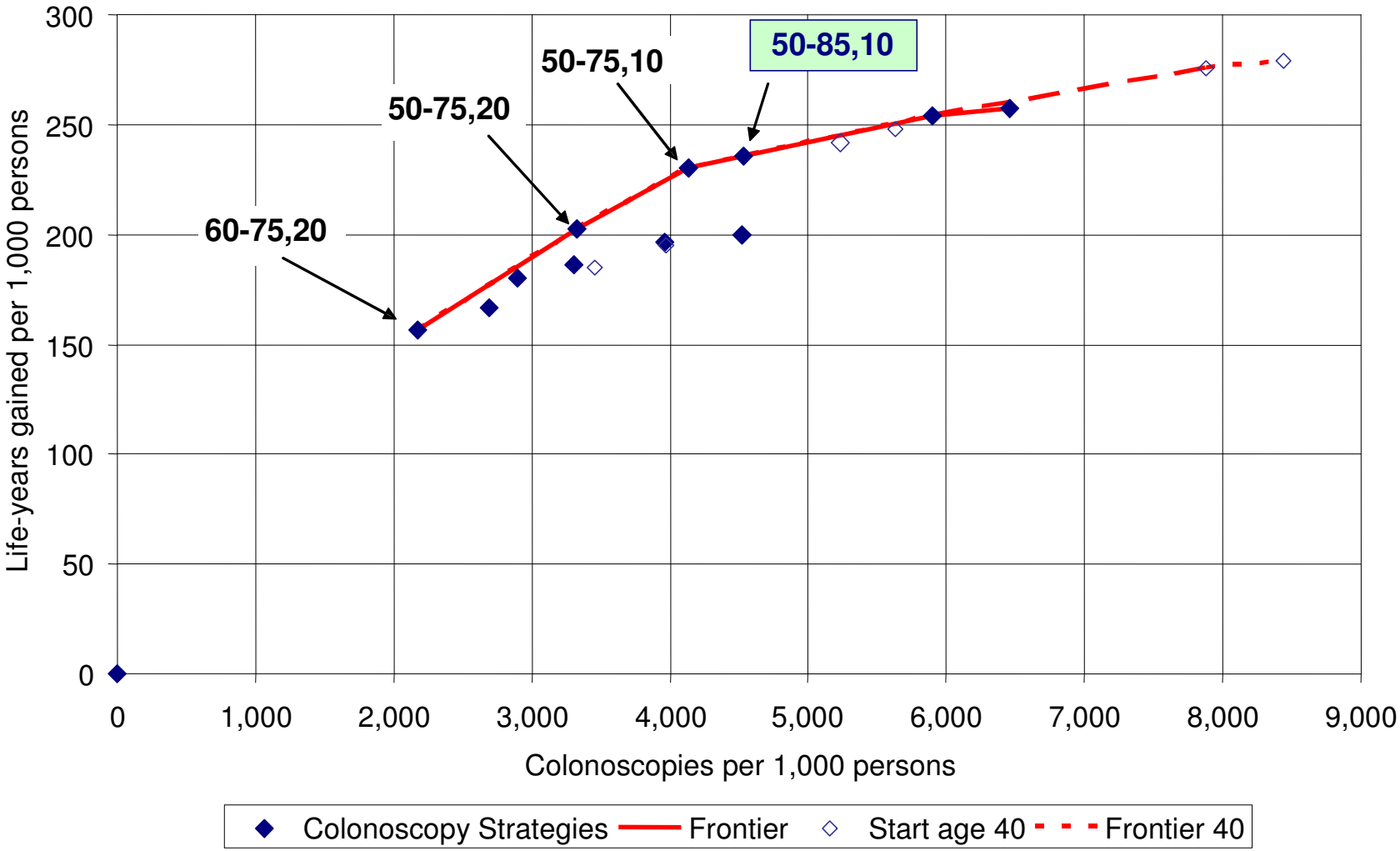
- A measure of the *additional* number of colonoscopies required to gain one year of benefit when considering a more effective strategy relative to the next less effective strategy
- Colonoscopy resources across tests are comparable but burden of *all testing* is not

Efficient Colonoscopy Strategies

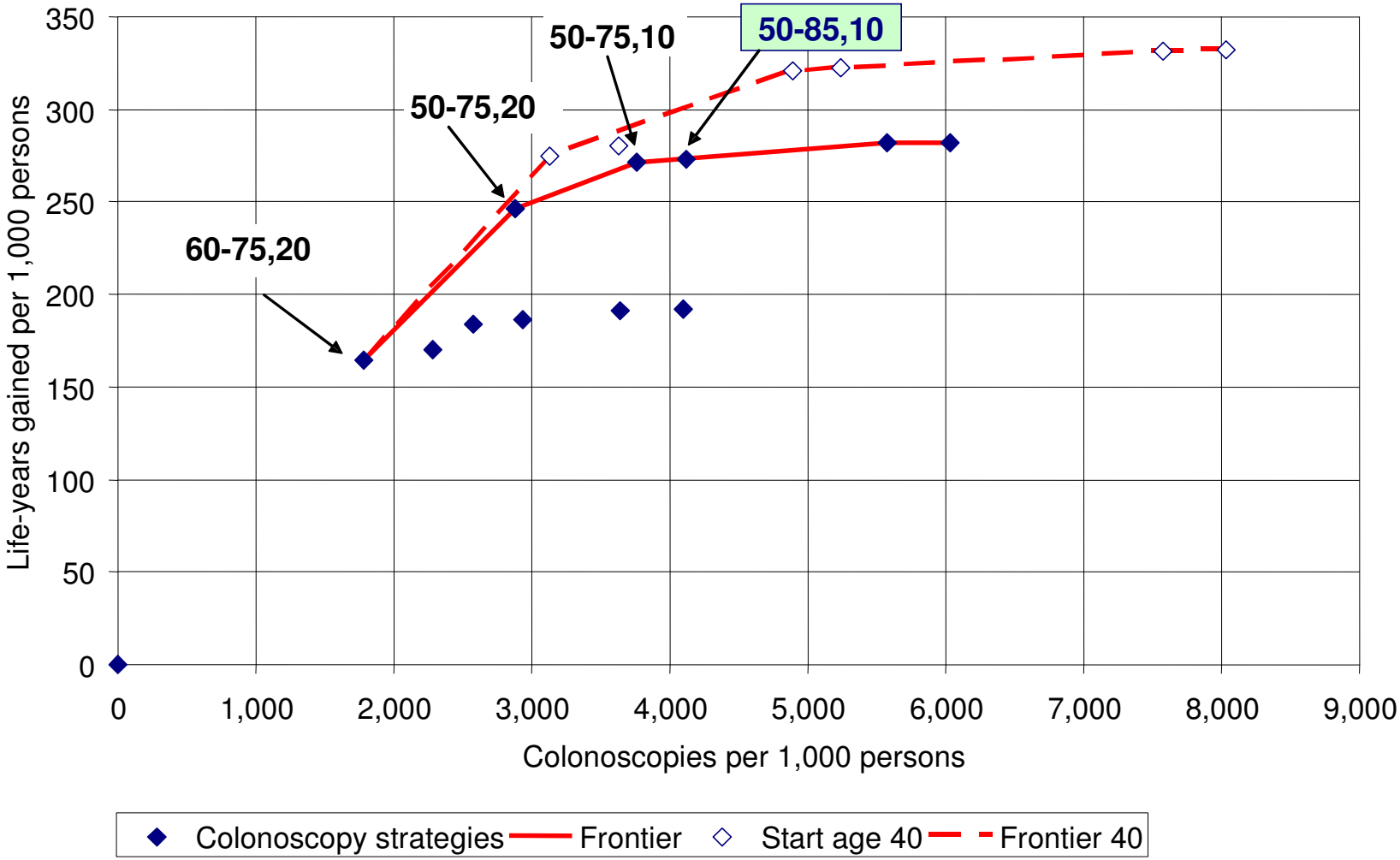
Strategy*		# Col (per 1000)	# LYG (per 1000)	ΔCol (per 1000)	ΔLYG (per 1000)	ΔCol/ΔLYG
MISCAN						
1	COL, 60-75, 20	2,175	156			---
2	COL, 50-75, 20	3,325	203	1,150	47	24.7
3	COL, 50-75, 10	4,136	230	811	27	29.6
4	COL, 50-85, 10	4,534	236	398	5	72.9
5	COL, 50-75, 5	5,895	254	1,362	18	74.8
6	COL, 50-85, 5	6,460	257	565	4	156.1
SimCRC						
1	COL, 60-75, 20	1,780	165			---
2	COL, 50-75, 20	2,885	252	1,106	82	13.5
3	COL, 50-75, 10	3,756	271	871	25	34.7
4	COL, 50-85, 10	4,114	281			ext dom
5	COL, 50-75, 5	5,572	293	1,816	10	178.8
6	COL, 50-85, 5	6,031	294	459	0.5	975.7

* Test, begin age – end age, interval
ΔCol = incremental number of colonoscopies compared with the next best strategy
ΔLYG = incremental number of life years gained compared with the next best strategy

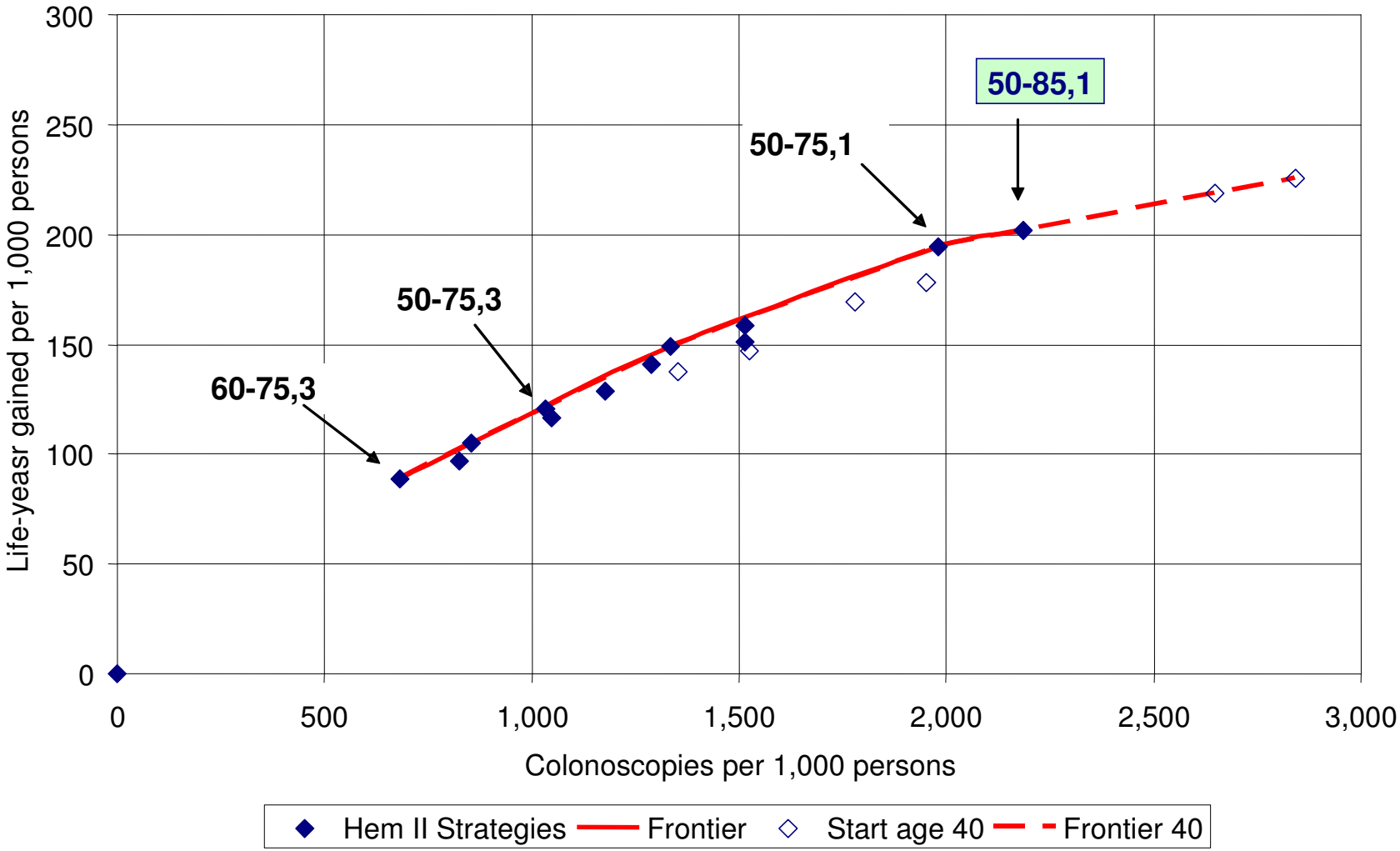
Colonoscopy-MISCAN



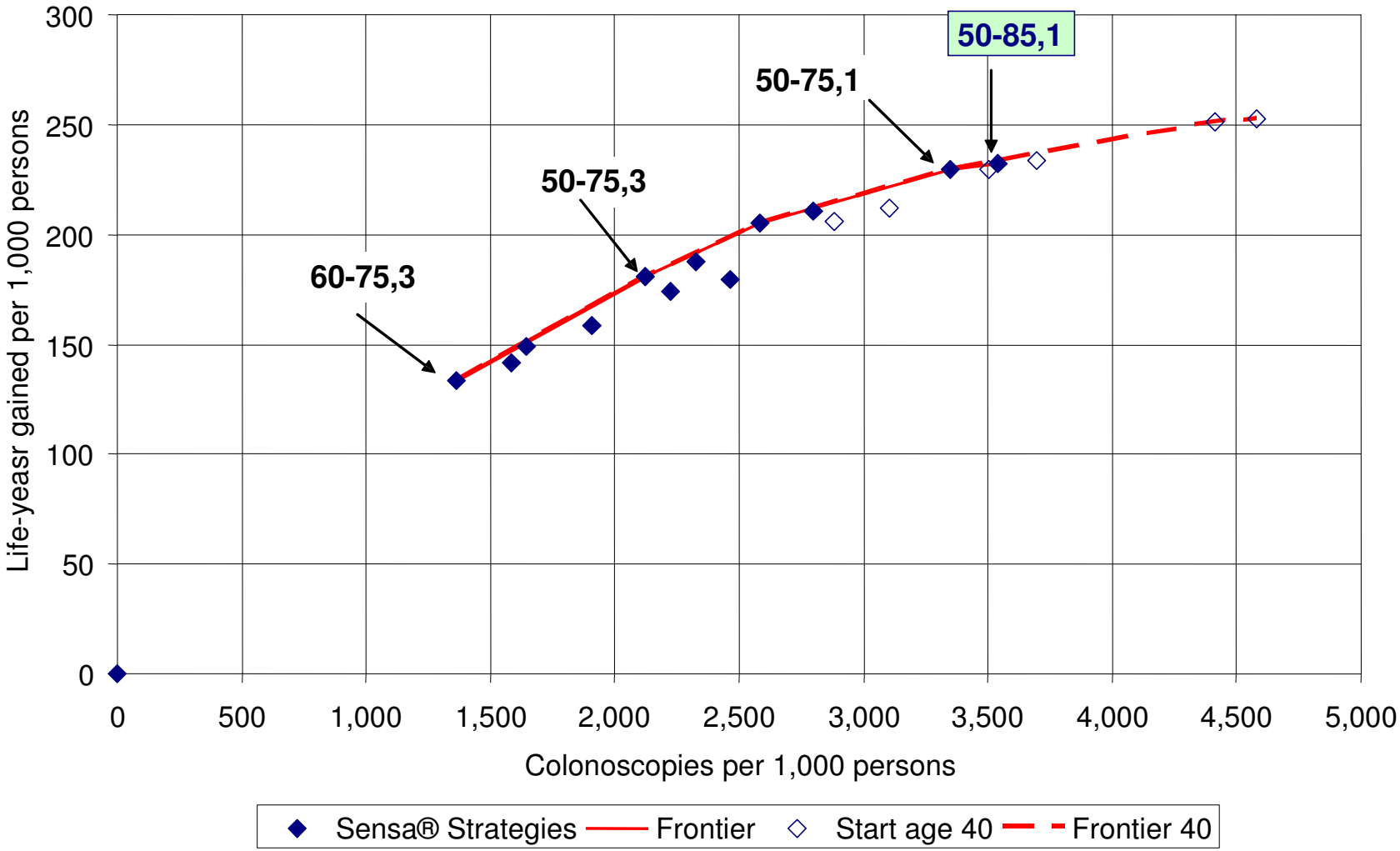
Colonoscopy-SimCRC



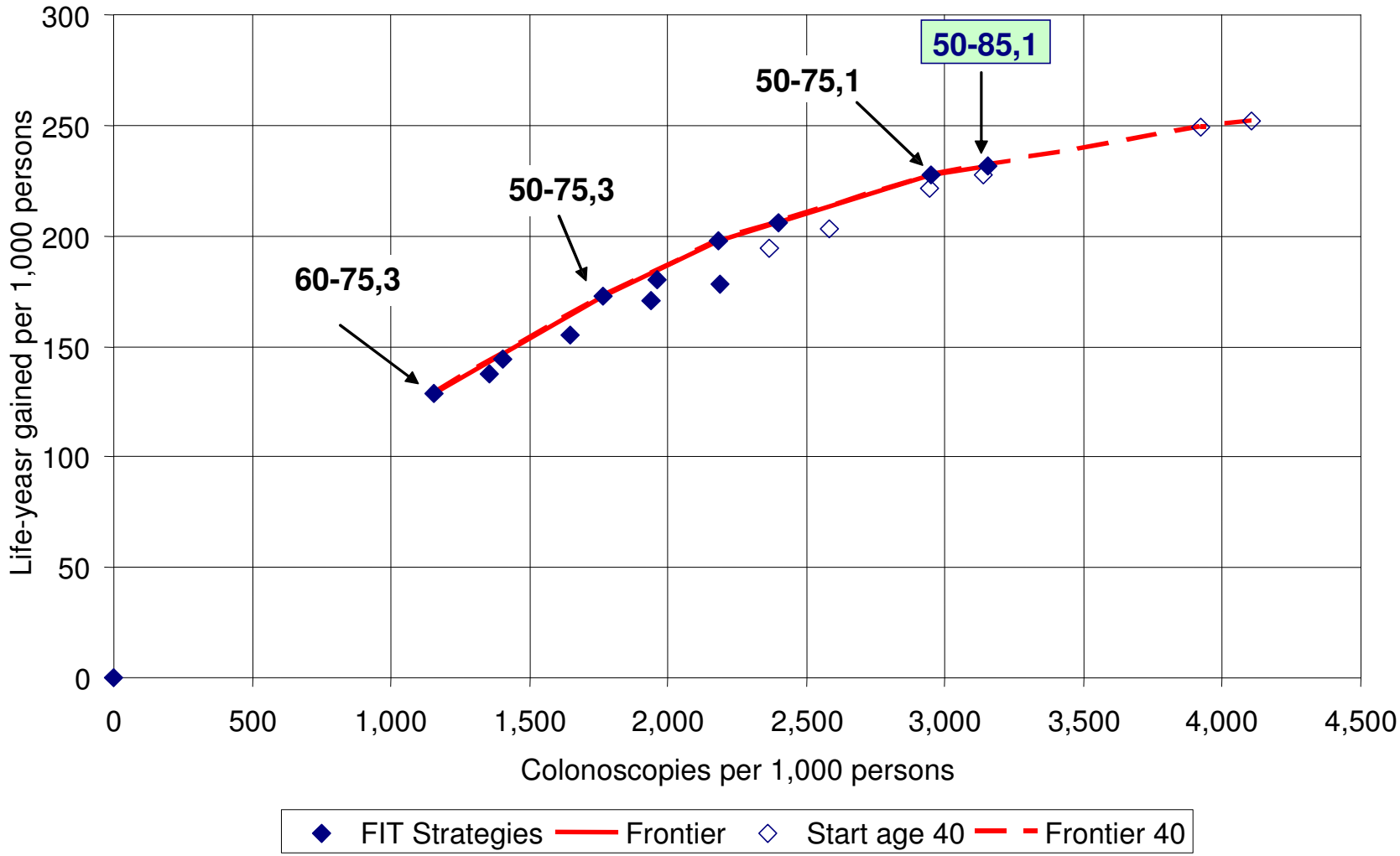
Hemoccult II-MISCAN



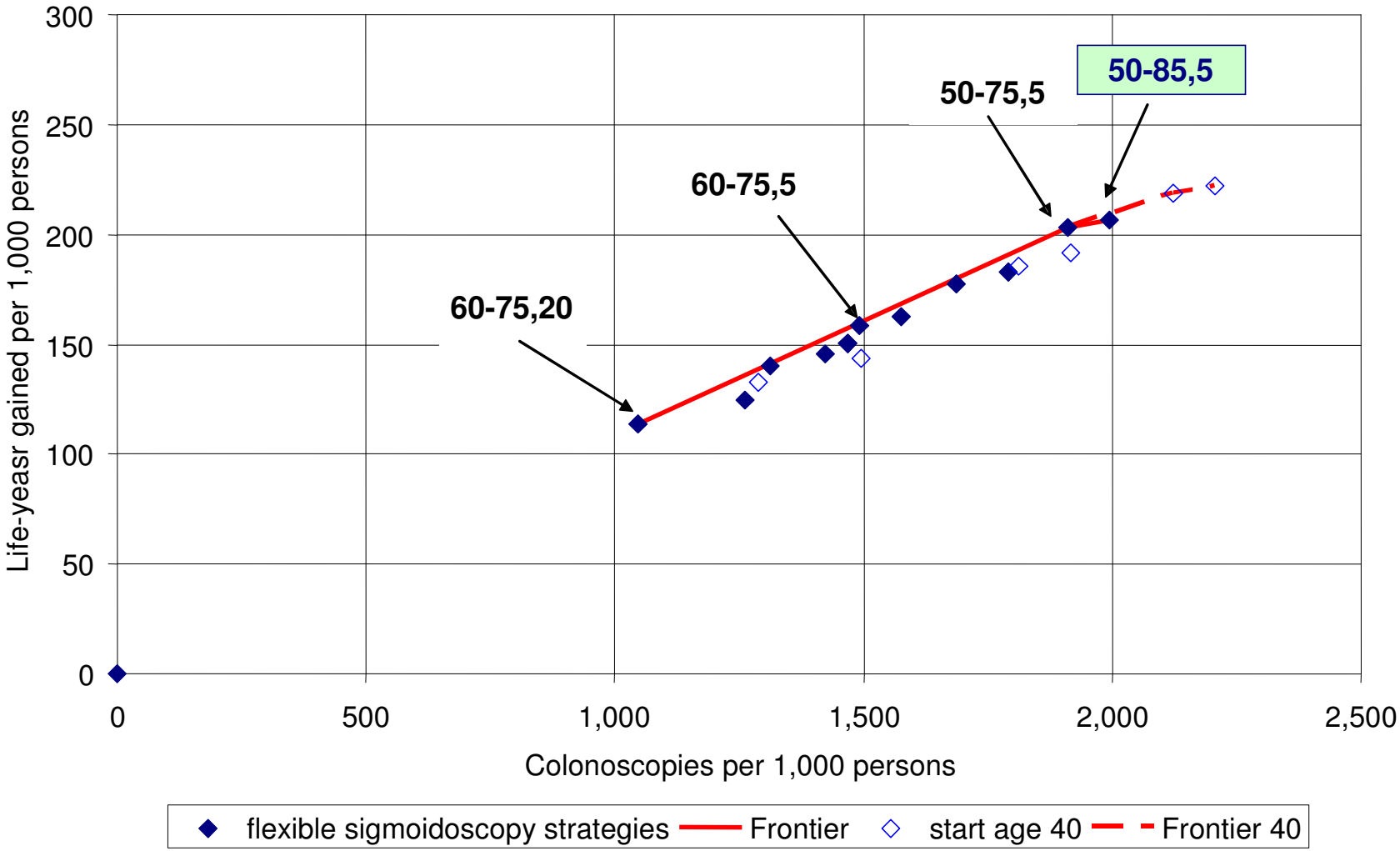
Hemoccult SENSA-MISCAN



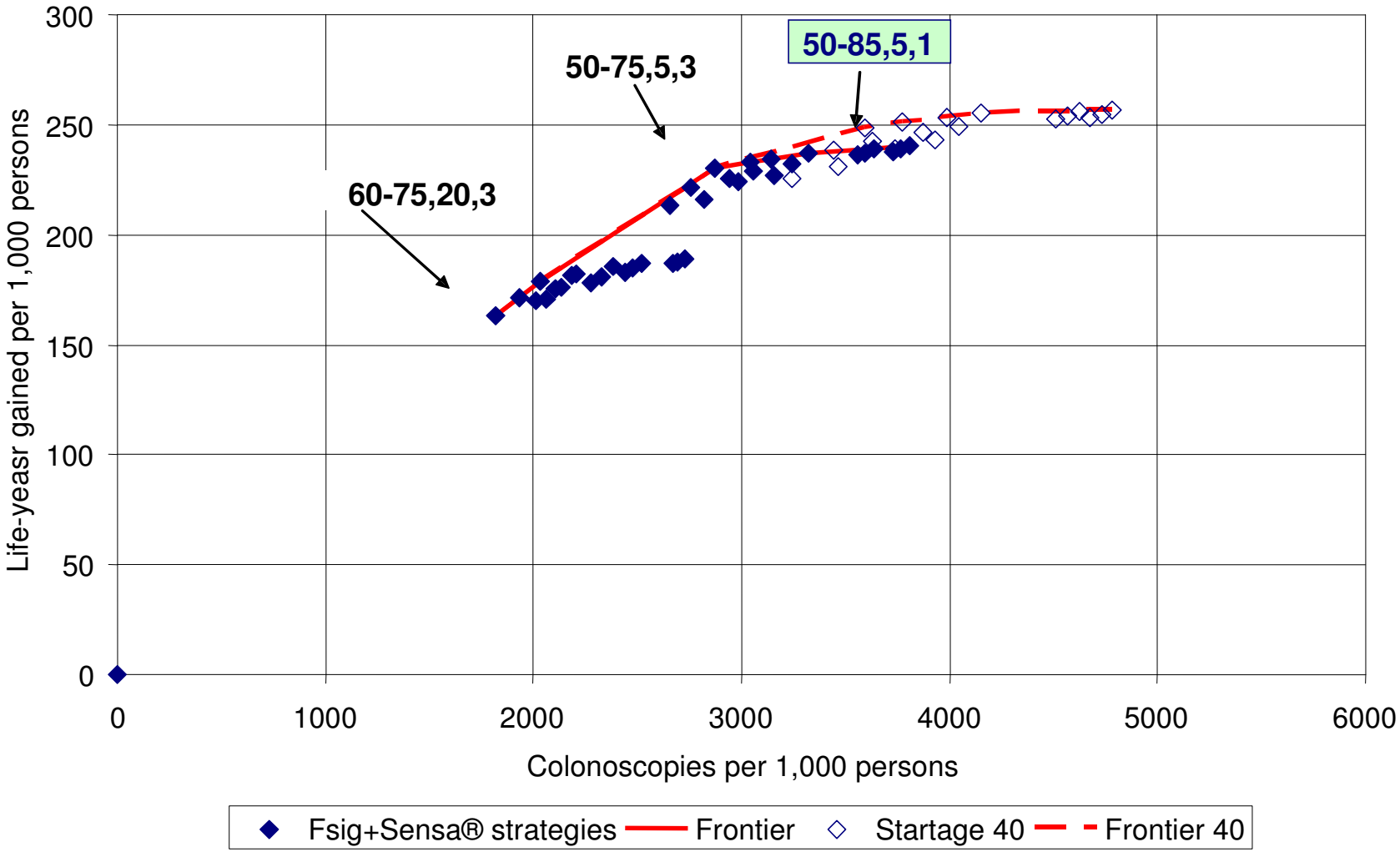
FIT-MISCAN


300
250
200
150
100
50
0
Life-yeasr gained per 1,000 persons
0
500
1,000
1,500
2,000
2,500
3,000
3,500
4,000
4,500
Colonoscopies per 1,000 persons
50-85,1
50-75,1
50-75,3
60-75,3
FIT Strategies
Frontier
Start age 40
Frontier 40

Flexible Sigmoidoscopy-MISCAN



Combination-MISCAN



Sensitivity Analyses

Best Case and Worst Case scenarios on sensitivity and specificity

- Worst case scenarios had lower life years gained than base case
- Best case scenarios had higher life years gained
- ΔCoI/ΔLYG lower for worst case and higher for best case for those on the efficient frontier

Mainly support the findings of the base case

Exceptions differ for the two models

Comparisons Among Tests

To compare among tests, it is important to consider that tests other than colonoscopy are required (ie, FOBT, Flex Sig)

To pick an efficient strategy for each test we would expect to find an ordering to the efficiency ratios as follows:

COL > SENSA > [FIT, HII] > [FSig, FSig+SENSA]

- Eg, SENSA should require *fewer* colonoscopies to gain a benefit of 1 year compared with COL because of the added number of FOBTs needed in addition to the colonoscopies to achieve that benefit.

Approach to Choosing Efficient Strategies

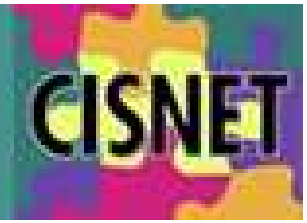
Assume that a single start and end age would be recommended for screening

Select strategies from all tests (including combination of tests) that:

1. are efficient (or near efficient) within the test
2. have efficiency ratios with expected ordering (to account for the burden of other testing)
3. have comparable effectiveness (LYG)

Example: start age = 50; stop age = 75; anchored with 10-year colonoscopy (as a starting strategy)

Efficient (near efficient) strategies for start age 50 and stop age 75-(Table 9 bolded strategies)



Strategy*	# Col (per 1000)	# LYG (per 1000)	ΔCol/ ΔLYG	# FOBT	# Fsig
MISCAN					
COL, 50-75, 10	**4,136**	**230**	**29.6**	**0**	**0**
SENSA®, 50-75, 1	**3,350**	**230**	**30.9**	**9,541**	**0**
FIT, 50-75, 1	**2,949**	**227**	**25.9**	**11,772**	**0**
Hem II®, 50-75, 1	**1,982**	**194**	**14.3**	**16,232**	**0**
Fsig, 50-75, 5	**1,911**	**203**	**9.7**	**0**	**4,139**
FsigSENSA®, 50-75, 5,3	**2,870**	**230**	**16.3**	**6,145**	
SimCRC					
COL, 50-75, 10	**3,756**	**271**	**34.7**	**0**	**0**
SENSA®, 50-75,1	**2,654**	**259**	**22.9**	**9,573**	**0**
FIT, 50-75,1	**2,295**	**256**	**19.7**	**11,830**	**0**
Hem II®, 50-75, 1	**1,456**	**218**	**9.6**	**16,239**	**0**
Fsig, 50-75, 5	**995**	**199**	**8.4**	**0**	**4,483**
FsigSENSA®, 50-75, 5,3	**1,655**	**257**	**7.0**	**9,679**	

‘Best’ Test is the One Which Gets Done- SJ Winawer re Adherence

Adherence: 80% and 50% by Screening Behavior Type

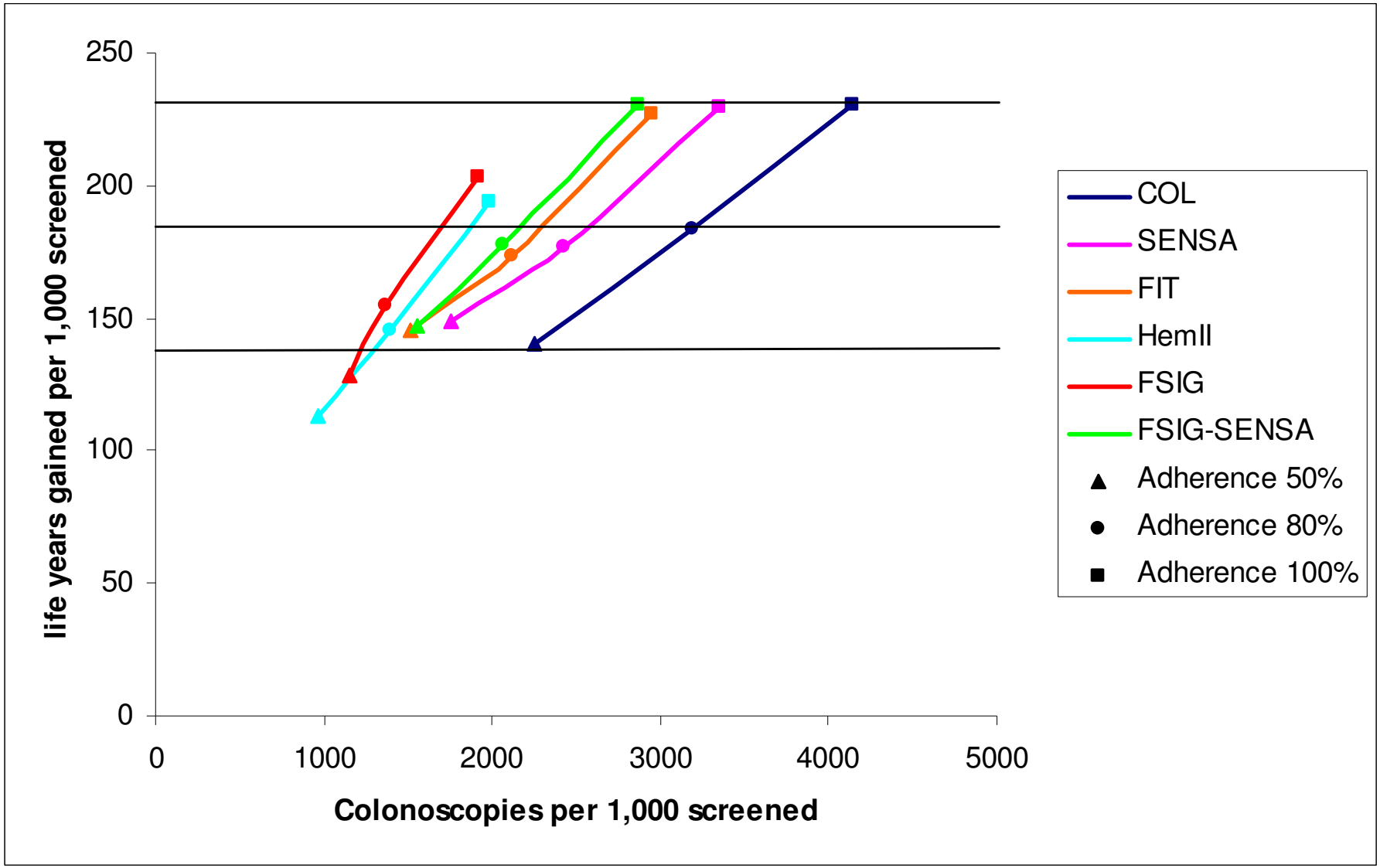
	Screening Behavior Group			
Overall Adherence	Never Screened (10%)	Low (30%)	Moderate (30%)	High (30%)
80%	0	0.78	0.89	1.00
50%	0	0.39	0.56	0.72
Follow-up Positive test	n/a	0.75	0.85	0.95
Surveillance	n/a	0.75	0.85	0.95

100% compliance for all also presented on graph

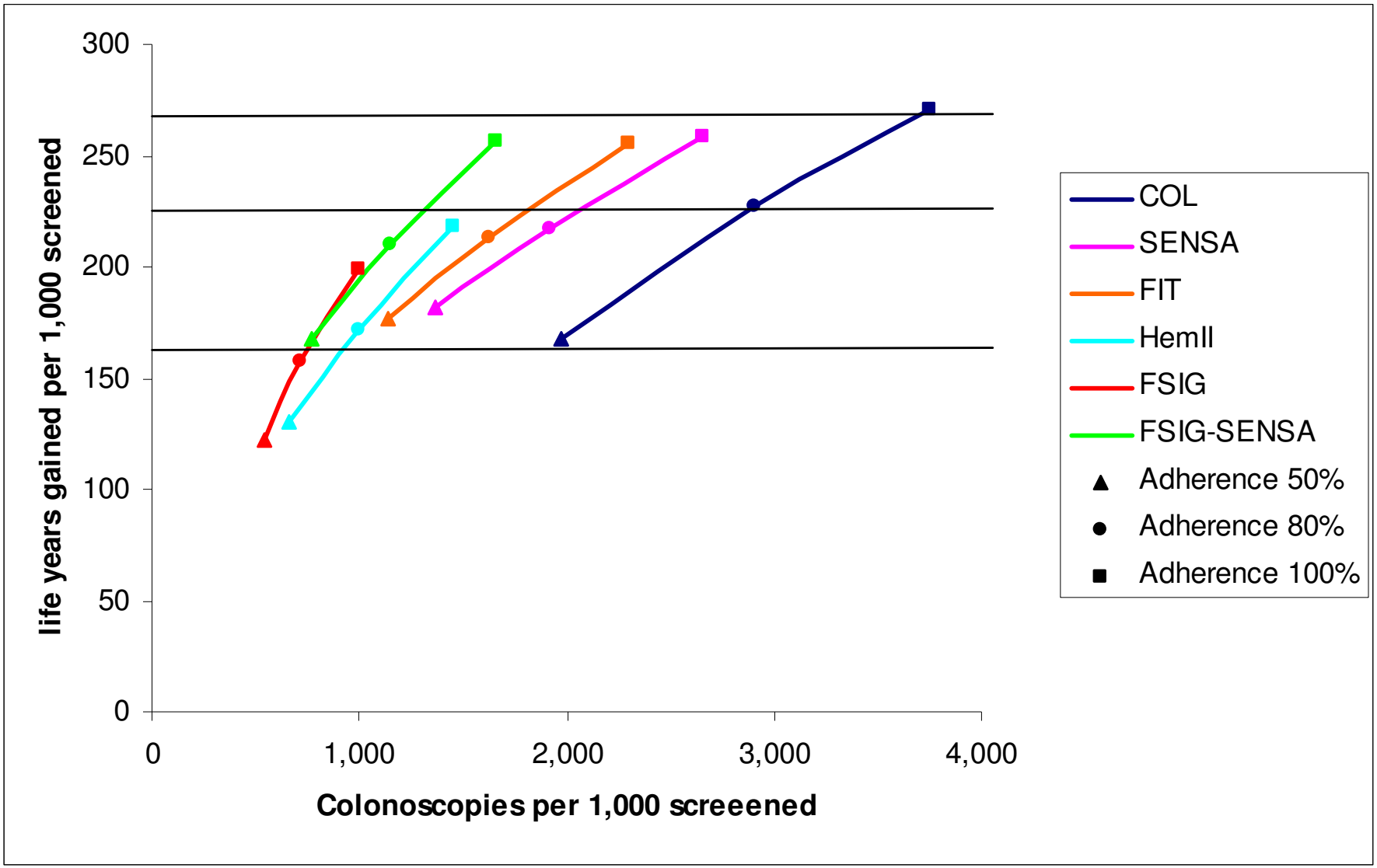
Bolded strategies varied by overall adherence to screening (Table 10)

	50% adherence		80% adherence		100% adherence	
Strategy	**# Col (per 1000)**	**# LYG (per 1000)**	**# Col (per 1000)**	**# LYG (per 1000)**	**# Col (per 1000)**	**# LYG (per 1000)**
MISCAN						
COL, 50-75, 10	2,250	140	3,193	184	4,136	230
SENSA®, 50-75, 1	1,752	149	2,427	177	3,350	230
FIT, 50-75, 1	1,510	145	2,116	173	2,949	227
Hem II®, 50-75, 1	962	113	1,395	145	1,982	194
Fsig, 50-75, 5	1,150	128	1,373	155	1,911	203
FsigSENSA®, 50-75, 5,3	1,553	147	2,063	178	2,870	230
SimCRC						
COL, 50-75, 10	1,977	168	2,904	227	3,756	271
SENSA®, 50-75, 1	1,361	182	1,920	217	2,654	259
FIT, 50-75, 1	1,140	177	1,629	213	2,295	256
Hem II®, 50-75, 1	666	130	993	172	1,456	218
Fsig, 50-75, 5	544	122	711	158	995	199
FsigSENSA®, 50-75, 5,3	770	168	1,153	210	1,655	257

MISCAN Adherence Plot



SimCRC Adherence Plot



Evidence Review from Oregon done *concurrently*

Reassessment of test parameters:

- Slight difference in specificity for Hemoccult SENSA
  - CISNET of 92.5%; ER of 87%
- Difference in sensitivity for Hemoccult II
  - CISNET of 40%; ER of 25%

Sensitivity analysis

- Specificity Hemoccult Sensa 87%
- Sensitivity Hemoccult II 20 and 25% with 95% Specificity

Results for Additional Sensitivity Analysis

Strategy MISCAN	# Col / 1000	# LYG / 1000
SENSA®, 50-75,1 (basecase)	3,350	230
SENSA®, 50-75,1 (87% specificity)	3,832 *(+14%)*	233 *(+1%)*
HII®, 50-75,1 (basecase)	1,942	194
HII®, 50-75,1 (95% Sp; 20% Se)	2,600 (+34%)	173 (-11%)
HII®, 50-75,1 (95% Sp; 25% Se)	2632 (+36%)	182 (-6%)

Strategy SimCRC	# Col / 1000	# LYG / 1000
SENSA®, 50-75,1 (basecase)	2,654	259
SENSA®, 50-75,1 (87% specificity)	3,104 *(+17%)*	263 *(+1.5%)*
HII®, 50-75,1 (basecase)	1,456	218
HII®, 50-75,1 (95% Sp; 20% Se)	2,016 (+38%)	181 (-17%)
HII®, 50-75,1 (95% Sp; 25% Se)	2,032 (+40%)	192 (-12%)

CONCLUSIONS of Modelers
NO decision by Task Force announced

Current recommended guidelines* are on or close to the efficiency frontier

Beginning at age 50 balances life years gained and number of colonoscopies required and associated risk of perforation

To increase efficiency of current guidelines*, stop screening at age 75

- *should depend on life expectancy of person rather than strict chronological age*

*MultiSociety and ACS

CONCLUSIONS (Continued 1)

Annual SENSA or FIT have similar LYG as colonoscopy every 10 years but with lower colonoscopy requirements – *PROVIDED high compliance for all tests*

FlexSig every 5 years with annual FOBT with Sensitive FOBT not recommended (high efficiency ratio)

- Original strategy for Flex Sig+ FOBT was for Hemoccult II with lower sensitivity
- Combination of Flex Sig and Hemoccult SENSA® could have one mid-interval FOBT between the 5 year repeat Flex Sig screening rather than annual FOBT

FlexSig every 5 years and Hemoccult II not as good in terms of effectiveness

CONCLUSIONS for Adherence

Adherence conclusions

- Life years gained and colonoscopies decreased with decreased adherence BUT
- The overall conclusions did not change substantially as adherence varied from 50% to 100%.

- Hemoccult II and flexible sigmoidoscopy every 5 years remained the least two attractive alternatives re life years gained
- Colonoscopy every 10 years improved a bit relative to the other strategies when adherence was 80% but lost its health benefit advantage when adherence as 50%

Limitations

Analyses for whole population – not specific by sex or race

- Potential of more proximal disease in older women and blacks
- Age of onset may vary by sex and race

Simulation models rely on assumptions of natural history of disease

- Comparing two models provides sensitivity analysis of natural history assumptions

"All models are wrong, some are useful."

- George Box, 1979

"I'd have been here sooner if it hadn't been for early detection."

COSTS

Screening

Complications

Colorectal Cancer Treatment

Thank You

Screening Costs for CMS (1)

Payer (CMS) and Society prospective

Per unit test –

- Guaiac FOBT $4.54 (Hemoccult II or SENSA)
- Immunochemical test $22.22
- *Note this from point of view of payer*

July 2001, Medicare coverage of colonoscopy every 10 years in average risk population

Screening Costs for CMS (2)

CPT codes for endoscopy tests

- Drs. John Allen and Joel Brill- gastroenterologists
- National unadjusted payment amounts under the physician fee schedule
- Unadjusted costs rather than RVUs
- Points of service ***(Bill Larson and Chuck Shih)***
  - Outpatient prospective payment system (OPPS)
  - Ambulatory Surgery Center (ASC) with associated facility charge
  - Physician fee schedule (PFS)
  - *No inpatient screening*
- Weighted average of screening procedure costs per point of service setting with inclusion of facility charges as allowed

Screening Costs for CMS (3)

Polypectomy and Pathology

- Polypectomy CPT codes (as above)
- Pathology costs per setting
  - Multiple polyps in one specimen jar per segment of colon
  - 1.38 times pathology fee to account for multiple specimens for patients with polyps (A Zauber personal communication from National Colonoscopy Study)

Incomplete colonoscopies

- Repeat the colonoscopy
- Assumed 5% required repeat colonoscopy to clear

Sedation –included in cost of colonoscopy

- Propofol sedation not included

Bowel prep not covered

Pre-visit not covered except for part of overall deductable

Screening Costs for CMS (4)

Weighted average of CPT code costs by percentage with procedures by point of service

Procedures could be overweighted for therapeutic colonoscopies rather than screening colonoscopy

Screening colonoscopy is a colonoscopy *planned* for screening and procedure with no polyps detected

Colonoscopy planned for screening but with polyps detected are classified as therapeutic colonoscopies

Currently can't get out just screening colonoscopies with and without polypectomy costs.

Table 3. Screening Tests Costs Based on the CMS cost reimbursement($2007)

Screening test	CMS cost, $	Societal cost, $
Guaiac Hemoccult (II or SENSA)	4.54	21.54
Immunochemical fecal occult blood test (FIT)	22.22	39.22
Flexible sigmoidoscopy	160.78	270.30
Flexible sigmoidoscopy with biopsy	348.19	497.37
Colonoscopy without polypectomy	497.59	834.69
Colonoscopy with polypectomy or biopsy	648.52	1,019.02

Complication costs

Literature review of complications

- General practice
- Screening studies
- Medicare data (Warren, Klabunde)

DRG codes for similar procedures because of complications

Physician fee not included because of difficulty in obtaining such from CMS reporting

Table 4. Summary of costs and risks of endoscopy complications

Complication	Rate per 1000	Cost, $2007
With colonoscopy		
Perforation	0.7	12,446
Serosal burn	0.3	5,208
Bleed with transfusion	0.4	5,208
Bleed without transfusion	1.1	320
With flexible sigmoidoscopy		
Perforation	0.02	12,446

SEER Medicare Link for CRC

Cost Data updated from 1998 – 2003 to 2007

- Hospital Wage Index and Medicare Economics Index used to adjust for inflation in Medicare parts A and B estimates
- Geographical variability in costs of care adjusted

New biological therapies sparsely represented in these data of 1998-2003

Phase specific costs of CRC

Cost of care used rather than billed charges

Payments for Medicare A (inpatient services) and B (outpatient services) calculated separately

Time costs for cancer care adjusted *(Yabroff 2007)*

Modified Societal Costs

Added copayments (beneficiary costs) and time costs to the payer costs

For cancer related costs, estimated patient deductibles and coinsurance expenses added by adjusting Part A and B payment with Medicare reimbursement ratios provided by CMS Office of the Actuary.

Table 5. Net payments for CRC care during 1998-2003 (in $2007)* Yabroff and Brown

			Last Year of Life	
AJCC Stage	Initial Phase	Continuing Phase	Died of Cancer	Died of Other Causes
Direct Medical Costs				
I	25,491	2,028	45,697	11,259
II	35,179	1,891	45,567	9,848
III	42,891	2,702	48,013	13,028
IV	56,009	8,377	64,438	34,980
Societal Costs				
I	28,668	2,395	51,935	12,703
II	39,700	2,237	51,712	11,035
III	48,951	3,249	54,776	14,708
IV	64,801	10,419	73,522	39,679

*The initial phase of care is the first 12 months following diagnosis, the last year of life phase is the final 12 months of life, and the continuing phase is all the months between the initial and last year of life phases. Cancer-related costs in the continuing phase of care are an annual estimate.

Cancer Care Costs for 2003 FIT Report

Initial Care	$26,800
Annual Continuing Cost	$2,100
Terminal Care Costs of those dying of CRC	$21,700

Based on 1990-1994 SEER Medicare case control and updated to 2002

Thank You