



P130001
Epi proColon[®] from Epigenomics AG

Molecular and Clinical Genetics Panel Meeting
March 26, 2014

FDA Presentation

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FDA Review Team

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Jack McCracken	Labeling

Overview of FDA Presentation

Part I: Background and Analytical Studies

- Rationale for Panel Meeting
- Regulatory History & Device Description
- Non-Clinical Studies

Part II: Clinical Studies

- Study Design and Analyses
- Factors influencing Test Performance
- Benefits vs. Risks

Part III: Review Considerations

- Test Performance / Scope of Claims
- Proposed Post-Approval Study

Rationale for Meeting

To obtain Panel input on:

- Safety and effectiveness of Epi proColon
- Whether the benefits outweigh the risks of using Epi proColon for the proposed intended use

PMA Regulatory History

- Dec 2011 - First module received
- Jan 2013 - Final module submitted (P130001)
- Feb 2013 - P130001 filed
Priority review granted
- Apr 2013 - Major deficiency letter issued
- Oct 2013 - Sponsor responses received
- Mar 2014 - Panel meeting

Proposed Intended Use

Epi proColon test is a qualitative *in vitro* diagnostic test for the detection of methylated Septin9 DNA in EDTA plasma derived from patient whole blood specimens. Methylation of the target DNA sequence in the promoter region of the SEPT9_v2 transcript has been associated with the occurrence of colorectal cancer (CRC). The test uses a real-time polymerase chain reaction (PCR) with a fluorescent hydrolysis probe for the methylation specific detection of the Septin9 DNA target.

The test is indicated to screen patients for colorectal cancer who are defined as average risk for colorectal cancer (CRC) by current CRC screening guidelines. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy. Men and women 50 to 85 years of age were included in Epi proColon clinical trial. Epi proColon test results, together with the physician's assessment of history, other risk factors, and professional guidelines, may be used to guide patient management.

Epi proColon test is for use with the Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument.

Proposed Warnings

- Not intended to replace colorectal screening by colonoscopy.
- A positive test result should be referred for diagnostic colonoscopy.
- Those with a negative test result should be advised to continue in a CRC screening program.
- Positive results have been observed in patients with chronic gastritis, lung cancer and in pregnant women.

Proposed Limitations

- Epi proColon is an alternative screening method for patients who are average risk for CRC, and who are unwilling, unable or do not undergo screening by other recommended methods.
- Test has not been evaluated in patients who are at higher risk for CRC.
- There is insufficient evidence to report programmatic sensitivity.
- Screening of persons over age 75 should be made on individual basis.

Device Description

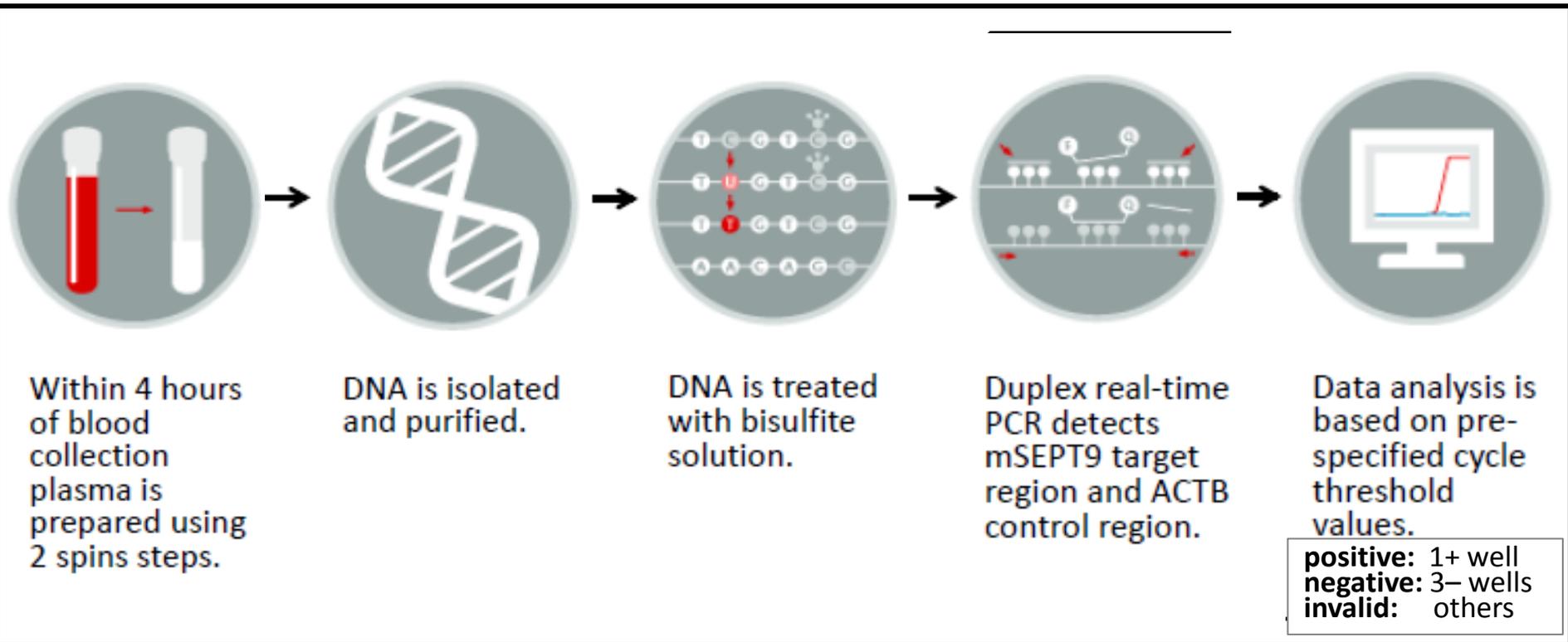
Epi proColon consists of 3 product kits:

- Epi proColon Plasma Quick Kit
- Epi proColon Sensitive PCR Kit
- Epi proColon Control Kit

Required components not included:

- BD Vacutainer K2 EDTA tubes
- ABI 7500 Fast Dx PCR instrument with Sequence Detection Software v1.4

Device Description



Adapted from <http://www.epiprocolon.com/en/laboratories/septin9-test/performing-the-test.html>

Non-Clinical Studies

- Analytical Sensitivity – Limit of Detection
- Analytical Specificity
 - Cross Reactivity
 - Interference
- Assay Cutoff Verification
- Reproducibility
- Guardbanding & Robustness
- Specimen handling, preparation, storage
- Stability

Non-Clinical Studies

- Analytical Sensitivity – Limit of Detection
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Cross Reactivity – Chronic Conditions

Chronic Condition	Test Positive		95% CI
	n	%	
Chronic gastritis	5/17	29	13, 53
Cardiovascular disease	3/17	18	6, 41
Arterial hypertension	18/103	17	11, 26
Other chronic diseases	9/55	16	9, 28
Hyperlipidemia	5/34	15	6, 30
Type II diabetes	1/21	5	0, 23

- Positivity rates are not significantly different from the overall proportion of positive results.
- 4 categories (n < 10) had positivity rates greater than those observed in the clinical studies for non-CRC.

Cross Reactivity - Cancers

Cancer	Test Positive		95% CI
	n	%	
Colorectal Cancer	19/22	86	67, 95
Lung Cancer	53/99	54	43, 64
Prostate Cancer	10/40	25	14, 40
Breast Cancer	4/22	18	7, 39

- 4 categories ($n < 10$) had positivity rates greater than those observed in the clinical studies for non-CRC.
- Proposed warning in product labeling for chronic gastritis and lung cancer, and in pregnant women

Reproducibility Study

- 3 sites, 6 operators, 3 lots, 3 instruments
- 14 sample pools:
 - 6 CRC pools
 - 5 diluted CRC pools
 - 3 healthy donor pools
- 12 repeated measurements obtained per pool
- Agreement with the expected test result is:
 - 98% (95% CI: 94, 99) for all CRC pools
 - 75% (95% CI: 59,86) for all healthy pools

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Clinical Studies

Two studies were performed:

1. Pivotal Study – Compare performance of Epi proColon to that of colonoscopy.
2. Supplemental Study – Compare the performance of Epi proColon and FIT to colonoscopy.

PRESEPT Study

PRESEPT Study Specimens

2008-2010

Target of 50 CRCs

**Plasma collected,
aliquoted & stored**

Diagnosis by Colonoscopy

Category		Description
Colorectal Cancer	CRC	Invasive colorectal adenocarcinoma (Stage I-IV).
Advanced Adenoma	AA	Adenomatous polyp(s) \geq 10 mm, adenomas with a villous component or high grade dysplasia (HGD)
Small Polyps	SP	Polyps < 10mm and without a villous component or HGD.
No Evidence of Disease	NED	No evidence of any of the above

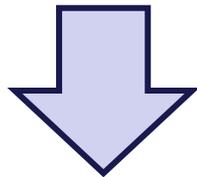
Academic Study (Church et al., 2013)

PRESEPT Study Specimens

2008-2010

Target of 50 CRCs

Plasma collected,
aliquoted & stored

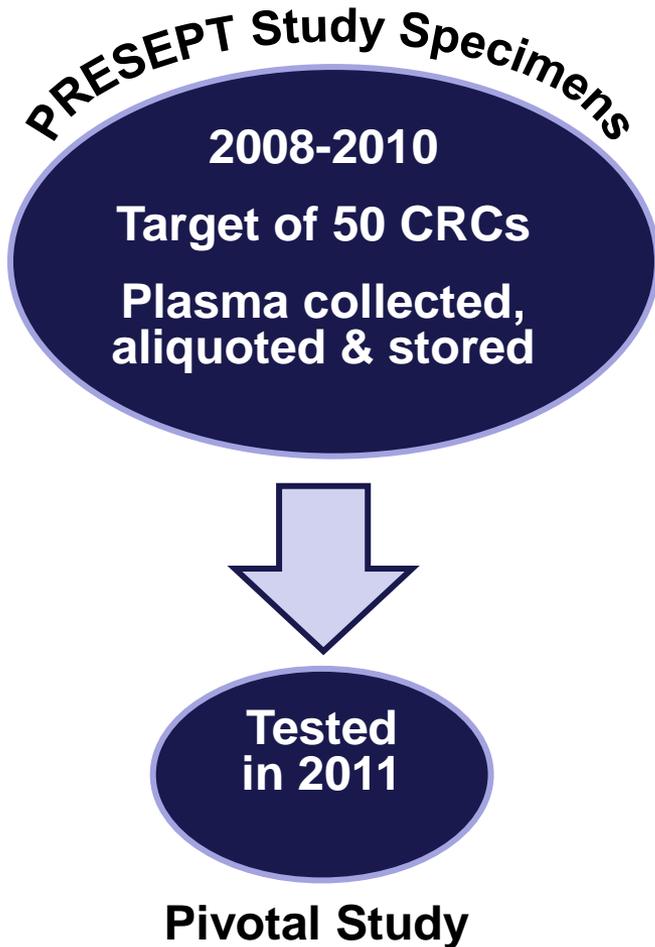


Published
2013

Academic Study

- A prospective evaluation of the Septin9 biomarker was conducted using the first generation assay (based on 2 PCR replicates).
- Included all CRC patients (n=53) and a subset of non-CRC samples (n= 1457) from PRESEPT.
- Sensitivity was 50.9% and specificity was 91.4%.

Pivotal Study



- Evaluation of the Septin9 biomarker was conducted with Epi proColon.
- Subsets of samples from the PRESEPT study were tested.
- 50 CRC (and a subset of AA) samples tested in the academic study were also used in the pivotal study.

Eligibility Criteria

PRESEPT - Inclusion Criteria

- Age 50 or older at time of colonoscopy
- Blood draw prior to colonoscopy
- First colonoscopy in lifetime

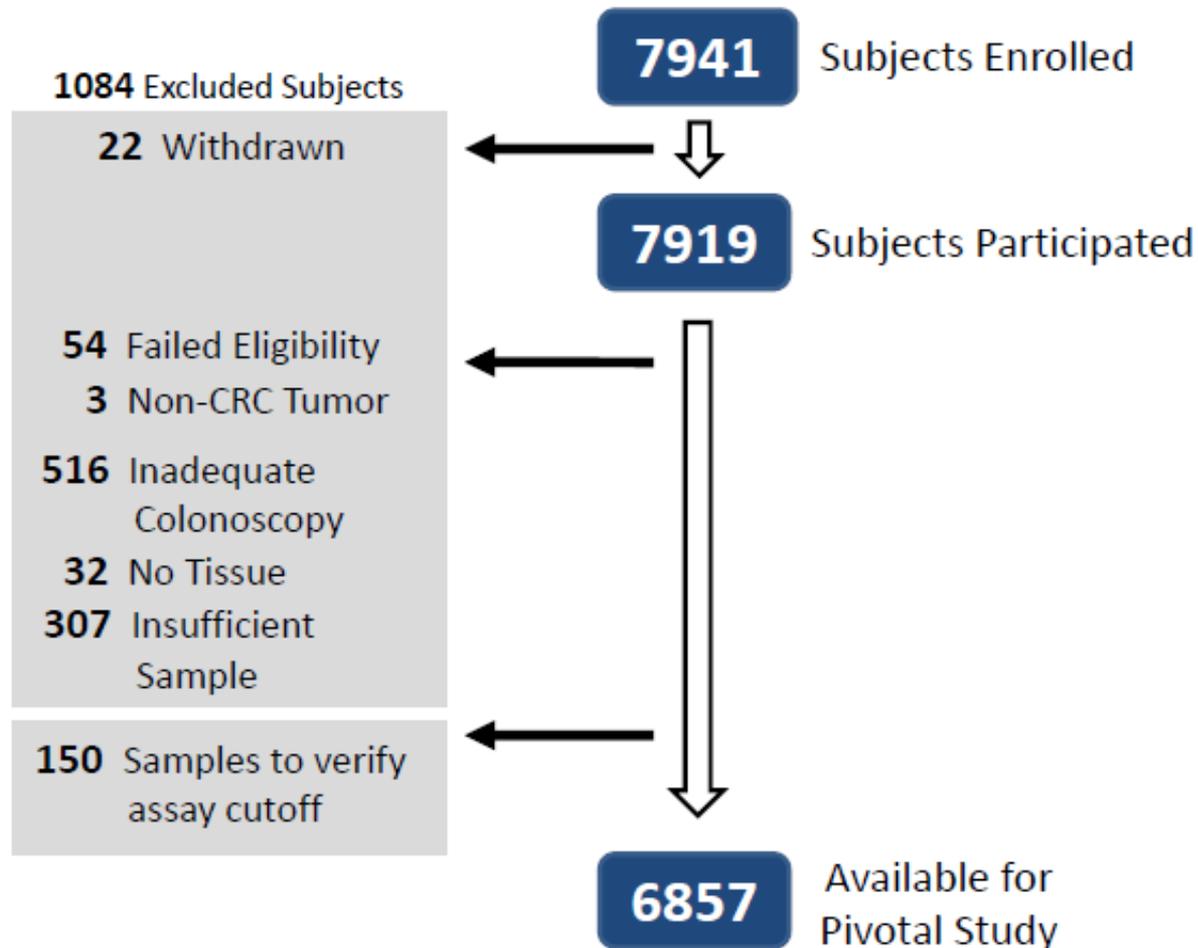
Exclusion Criteria

- Anorectal bleeding or hematochezia within last 6 months
- Iron deficiency anemia in the last 6 months
- High risk for colorectal cancer

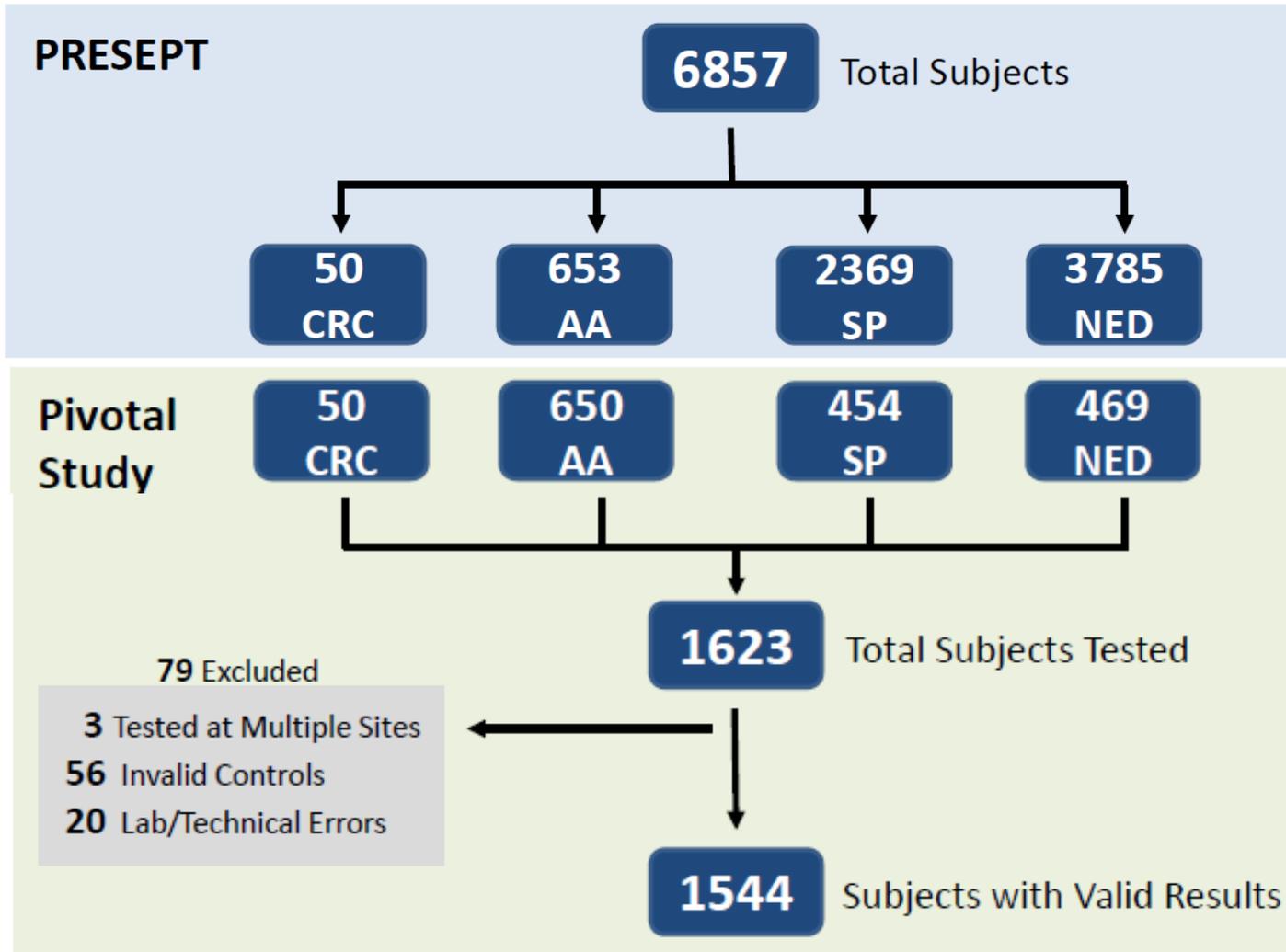
PIVOTAL STUDY - Exclusion Criteria

- Gross hemolysis (bright orange or red color)
- Protocol deviations
- Inadequate plasma volume

Subject Accountability - PRESEPT



Subject Selection – Pivotal Study



Pivotal Study Objectives (FDA)

- Epi proColon shall demonstrate sensitivity for CRC of 65%.
 - Lower bound of the two-sided 95% CI for sensitivity should be above 65%.
- Epi proColon shall demonstrate specificity of 85%.
 - Lower bound of the two-sided 95% CI for specificity should be above 85%.

Pivotal Study Results

Epi proColon	CRC	AA	SP	NED
Negative	14	487	348	347
Positive	30	134	87	97

- Sensitivity Study Goal: 65%

Sensitivity: 68.2% (95% CI: 53.4%, 80.0%)

95% CI lower bound below 65%. **FDA interpreted goal not met**
- Specificity Study Goal: 85%

Specificity: 78.8% (95% CI: 76.7%, 80.8%)

95% CI lower bound below 85%. **FDA interpreted goal not met**

Adjusted Predictive Values (FDA)

Prevalence in PRESEPT (n=6857)	Point Est (%)
CRC	0.7
Non-CRC	99.3
AA	9.5
SP	34.6
NED	55.2

Parameter	Point Est (%)	95% CI
Positive Predictive Value	2.3	1.8, 2.9
Negative Predictive Value	99.7	99.6, 99.8
P(AA negative)	9.5	9.1, 9.9
P(SP negative)	35.2	33.8, 36.7
P(NED negative)	55.0	53.4, 56.5

- PPV (2.3%) is 3.3 times larger than CRC prevalence
- Among patients that test negative, probability of AA, SP or NED is similar to prevalence of AA, SP and NED, respectively.

Secondary Objective

False Positive Fraction (1- specificity), non-CRC

Group	Proportion	Point Est (%)	95% CI
AA	134/621	22	19,25
SP	87/435	20	17,24
NED	97/444	22	18,26
Total	318/1500	21	19,23

- Variation of false positive fraction by non-CRC group was not significant ($p=0.76$)**
- Comparable False Positive Fraction: AA, NED

** *Significance level=5%*

Factors Influencing Test Performance

- Subgroup analyses should be interpreted with caution.
- Pivotal study not designed to evaluate test performance in subgroups.

False Positive Fraction (1-specificity) by Age Group, non-CRC

Age	Proportion	Point Est (%)	95% CI
50-59	100/611	16	14, 20
60-69	130/552	24	20, 27
70+	88/337	26	22, 31

- Increase in false positive fraction (decrease in specificity) with increasing age ($p < 0.001$).

False Positive Fraction (1-specificity) by Age Group, non-CRC (FDA)

Age	Proportion	Point Est (%)	95% CI
50-75	288/1404	20.5	18.5, 22.7
>75	30/96	31.2	22.9, 41.1

- Significant increase in false positive fraction, i.e., decrease in specificity (p=0.02).

False Positive Fraction (1-specificity) by Ethnicity, non-CRC

Ethnicity	Proportion	Point Est (%)	95% CI
Other	27/149	18	13, 25
Caucasian	221/1093	20	18, 23
African-American	70/258	27	22, 33

- Variation by ethnicity was significant ($p=0.035$).

False Positive Fraction (1-specificity) by Other Factors, non-CRC

- Other factors were reviewed
 - Gender (Male vs. Female)
 - Site (US vs. Germany)
- Variation by each of these factors was not significant

CRC Sensitivity by Site (FDA)

- Sensitivity: Germany 15/18 (83%)
 US 15/26 (58%)
- Difference in sensitivity is not statistically significant ($p=0.10$)

CRC Sensitivity by Other Factors

- Other factors were reviewed:
 - Location (Proximal vs. Distal)
 - Gender (Male vs. Female)
 - Age group (50-59, 60-69, 70+)
 - Ethnicity (Caucasian, African-American, Other)
- Variation by each of these factors was not significant

Pivotal Study Summary

- Sensitivity Goal: 65%
Estimated Sensitivity: 68.2% (95% CI: 53.4%, 80.0%)
95% CI lower bound below 65%. **FDA interpreted goal not met**
- Specificity Goal: 85%
Specificity: 78.8% (95% CI: 76.7%, 80.8%)
95% CI lower bound is below 85%. **FDA interpreted goal not met**
- Age and ethnicity significantly affect specificity in non-CRC subjects.
- Test performance in subjects who would not participate in screening colonoscopy cannot be determined from this study.

Clinical Studies

Two studies were performed:

1. Pivotal Study – Compare performance of Epi proColon to that of colonoscopy.
2. Supplemental Study – Compare the performance of Epi proColon and FIT to colonoscopy.

Study Design

Group A

- Subjects recruited retrospectively
- CRC at colonoscopy (stages I, II, III, IV).
- Blood and stool collected **after** colonoscopy, but prior to surgery or intervention.**

Group B

- Subjects enrolled prospectively
- Blood and stool collected **before** colonoscopy.

***Sample collection prior to colonoscopy would be consistent with the intended use.*

Eligibility Criteria – Group A

Inclusion Criteria

- Age 50-84 at specimen sampling
- Diagnosis by colonoscopy or strong clinical suspicion of CRC
- Colonoscopy within 6 months before inclusion into study
- Specimens sampling a minimum of 10 days after colonoscopy

Exclusion Criteria

- Curative biopsy during colonoscopy
- High risk for CRC
- Neoadjuvant treatment
- History of inflammatory bowel disease
- Current diagnosis of cancer other than CRC
- Acute or chronic gastritis
- Overt rectal bleeding or bleeding hemorrhoids

Eligibility Criteria – Group B

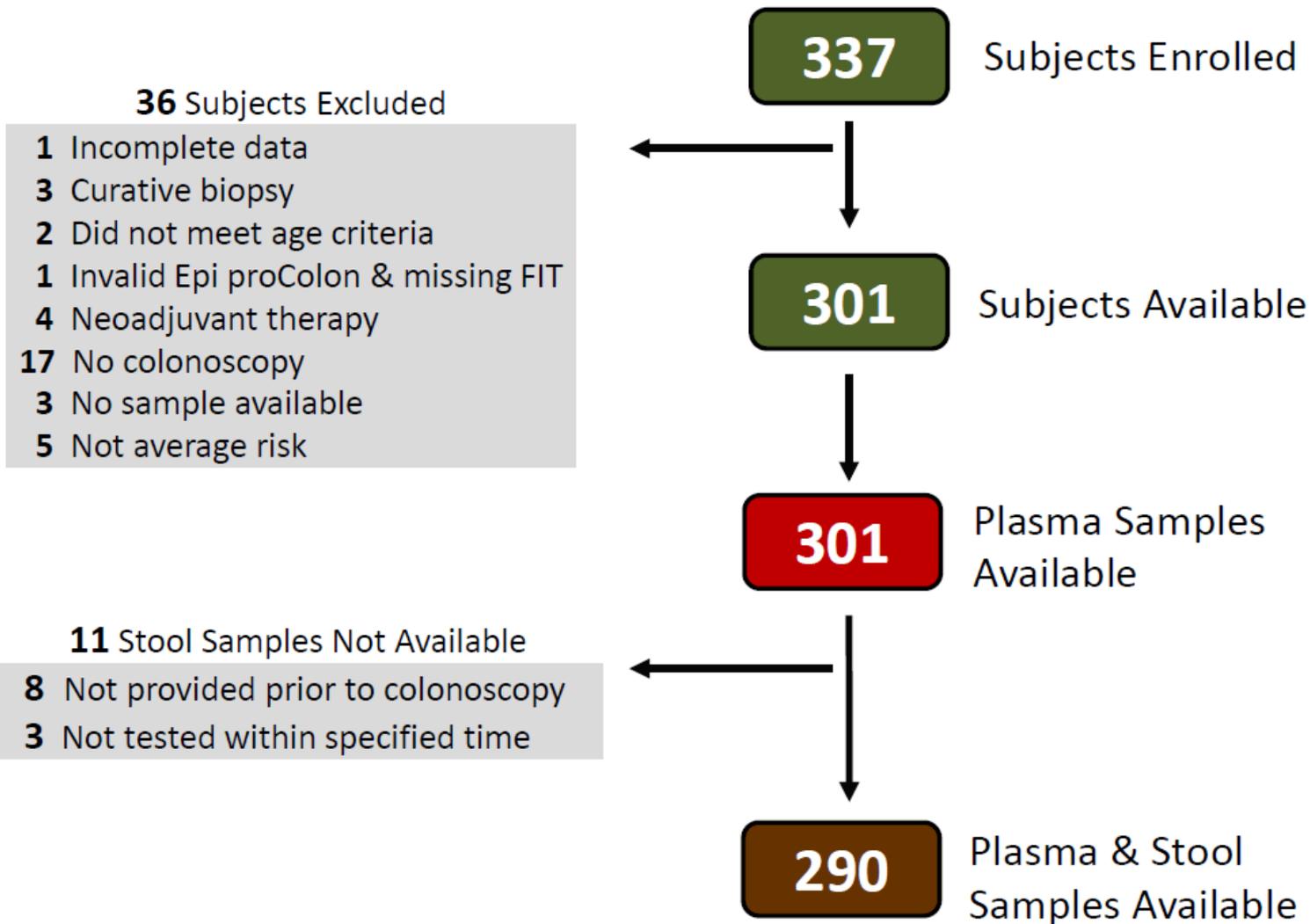
Inclusion Criteria

- Age 50-84 at specimen sampling
- Able to provide specimen samples prior to bowel preparation

Exclusion Criteria

- High risk for CRC
- Neoadjuvant treatment
- History of inflammatory bowel disease
- Current diagnosis of cancer other than CRC
- Acute or chronic gastritis
- Overt rectal bleeding or bleeding hemorrhoids

Subject Accountability



Study Objectives

Non-inferiority of Epi proColon compared to FIT:

- In CRC subjects, one-sided 95% CI for the difference in sensitivity is below 10%.
- In non-CRC subjects, one-sided 95% CI for the difference in specificity is below 20%.

*** At FDA request, two-sided 95% CIs were provided.*

Study Results - Sensitivity

		Proportion	Point Est (%)	95% CI
Epi proColon	Sensitivity	70/97	72.2	62.5, 80.1
	Specificity	156/193	80.8	74.7, 85.8
FIT	Sensitivity	66/97	68.0	58.2, 76.5
	Specificity	188/193	97.4	94.1, 98.9
Difference	Sensitivity	--	- 4.2	-16.2, 8.1
	Specificity	--	16.6	10.6, 22.9

- Non-inferiority **goal for sensitivity was met**

Study Results - Specificity

		Proportion	Point Est (%)	95% CI
Epi proColon	Sensitivity	70/97	72.2	62.5, 80.1
	Specificity	156/193	80.8	74.7, 85.8
FIT	Sensitivity	66/97	68.0	58.2, 76.5
	Specificity	188/193	97.4	94.1, 98.9
Difference	Sensitivity	--	- 4.2	-16.2, 8.1
	Specificity	--	16.6	10.6, 22.9

➤ Non-inferiority **goal for specificity was not met**

Comparison - Diagnostic Likelihood Ratios (DLR)

DLR+: ratio of true positive fraction to false positive fraction

DLR-: ratio of false negative fraction to true negative fraction

Metric	Epi proColon	FIT	Difference (95% CI)
DLR+	3.76	26.26	22.50 (9.45, 127.40)
DLR-	0.34	0.33	0.01 (-0.16, 0.12)

- Increase in DLR+ implies greater PPV with FIT (significant)
- Essentially no change in DLR- implies no change in NPV with FIT (not significant)
- Results do not depend on prevalence

“Believe the positive” (Epi ProColon+ or FIT+)

		Proportion	Point Est (%)	95% CI
Epi proColon	Sensitivity	70/97	72.2	62.5, 80.1
	Specificity	156/193	80.8	74.7, 85.8
FIT	Sensitivity	66/97	68.0	58.2, 76.5
	Specificity	188/193	97.4	94.1, 98.9
Difference	Sensitivity	--	- 4.2	-16.2, 8.1
	Specificity	--	16.6	10.6, 22.9
Believe the positive	Sensitivity	86/97	88.7	80.8, 93.5
	Specificity	152/193	78.8	72.4, 83.9

Epi proColon vs. “Believe the positive” Combination Using DLR (FDA)

DLR+: ratio of true positive fraction to false positive fraction

DLR-: ratio of false negative fraction to true negative fraction

Metric	Epi proColon	Combination	Difference (95% CI)
DLR+	3.76	4.17	0.41 (-0.19, 0.99)
DLR-	0.34	0.14	-0.20 (-0.30, -0.11)

- DLR+ ↑ implies greater PPV with combination (not significant)
- DLR- ↓ implies greater NPV with combination (significant)
- Results do not depend on prevalence

Association Epi proColon and FIT (FDA)

- No evidence was found that Epi proColon and FIT are not conditionally independent given disease status.

CRC		Epi proColon		
		+	-	Total
FIT	+	50	16	66
	-	20	11	31
	Total	70	27	97

(p=0.33)

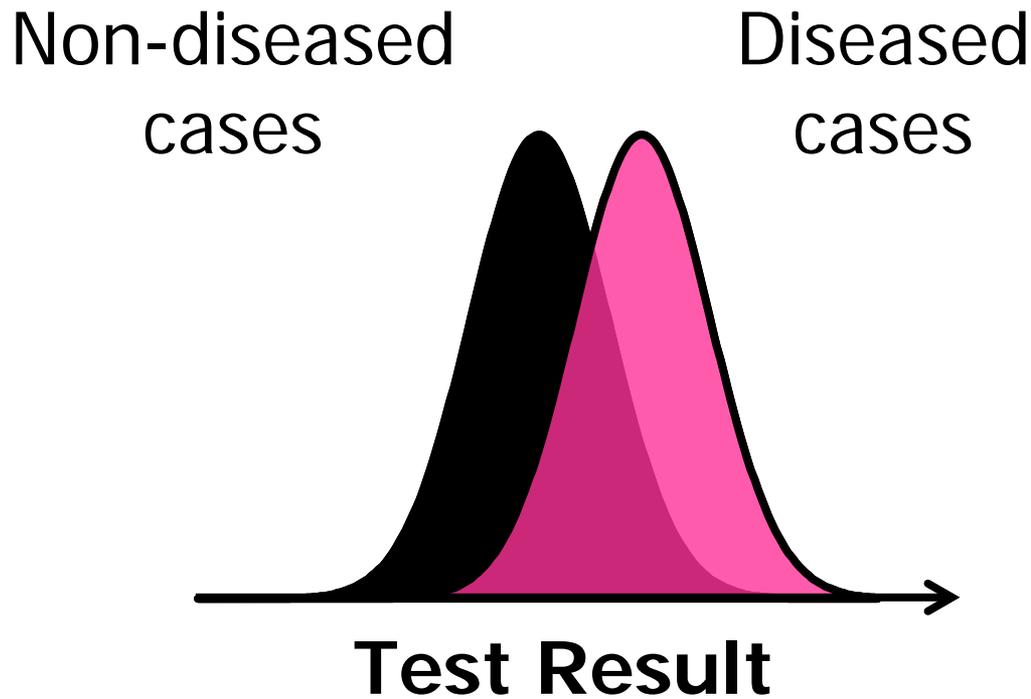
Non-CRC		Epi proColon		
		+	-	Total
FIT	+	1	4	5
	-	36	152	188
	Total	37	156	193

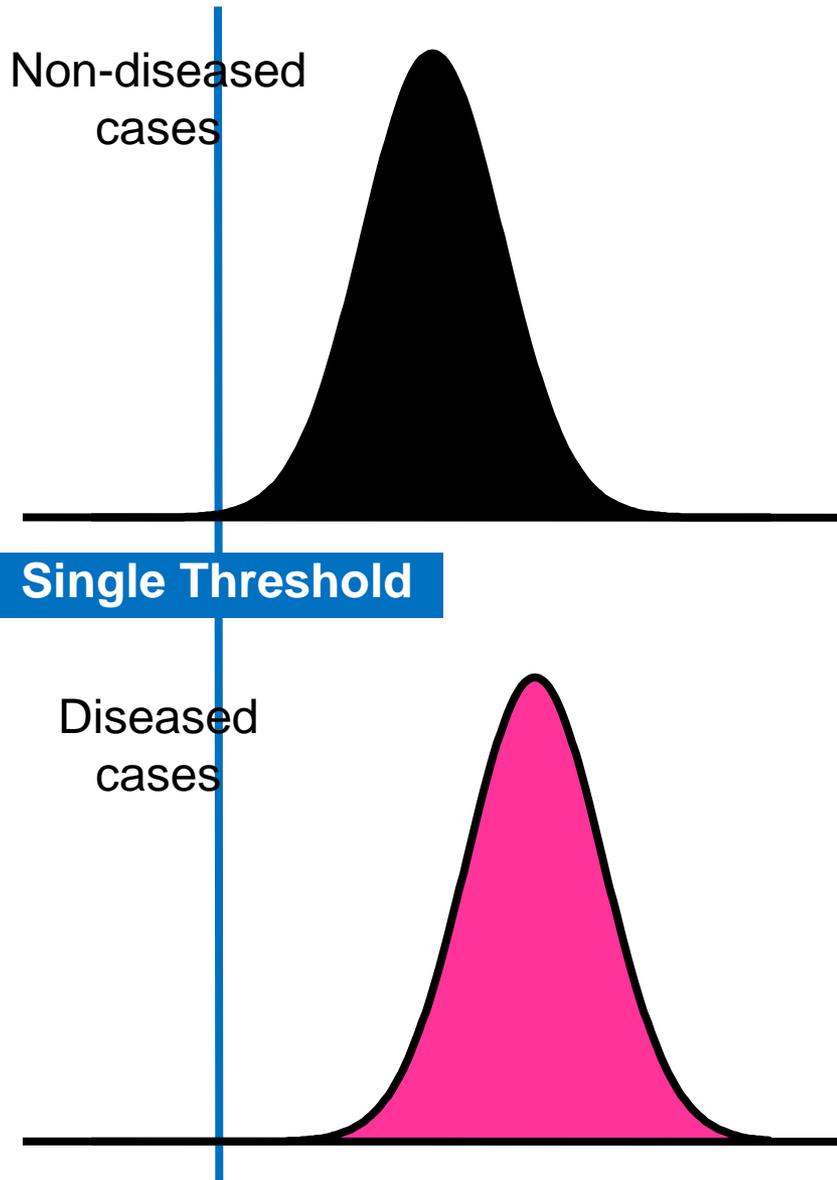
(p=1.00)

Intent-to-Diagnose (ITD) Analysis

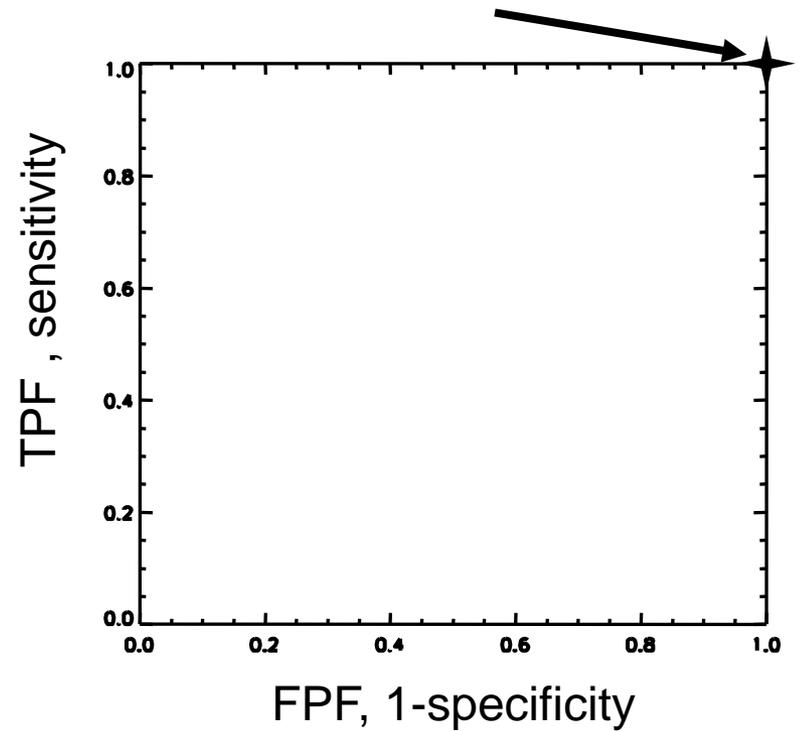
- 301 plasma samples available
- 290 stool samples available
- To account for the 11 subjects with missing FIT results, an analysis was conducted by imputing the missing FIT results.
- The study results (non-inferiority of Epi proColon to FIT was met for sensitivity, but not for specificity) were robust to the missing data.

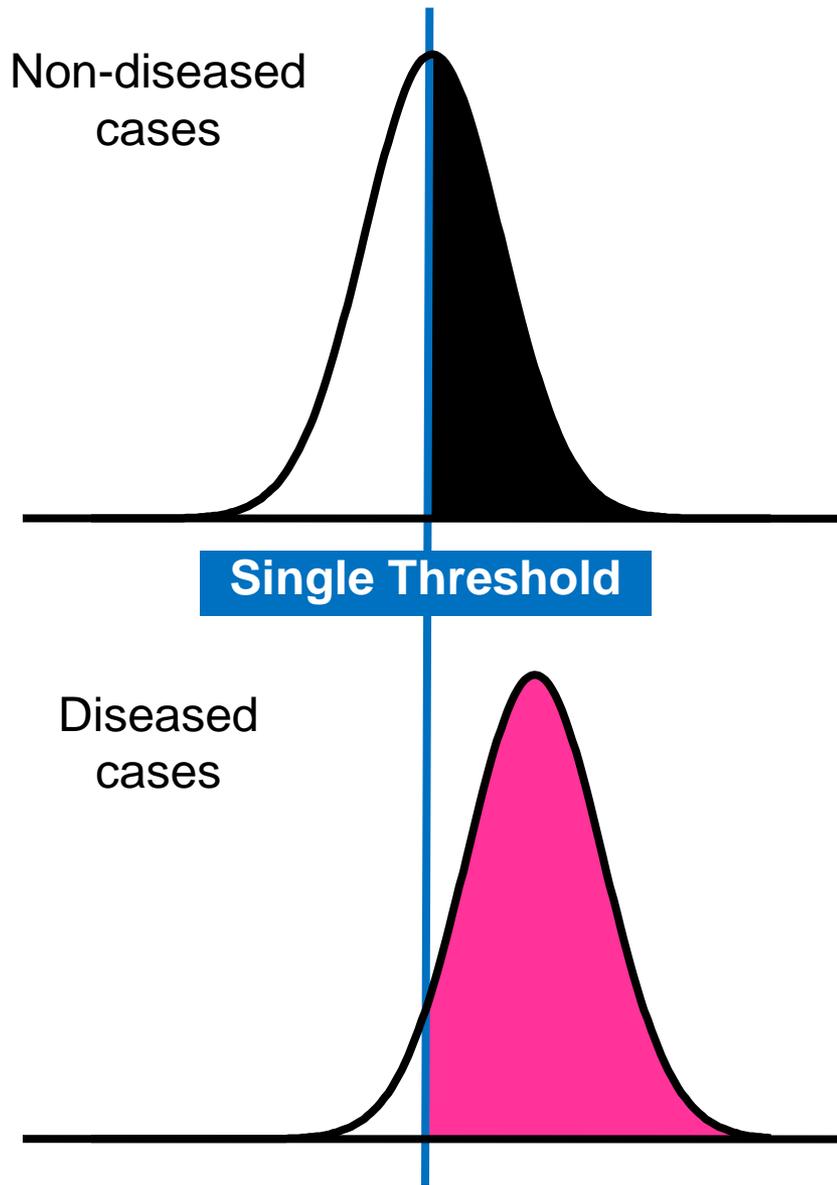
ROC Curve Analysis



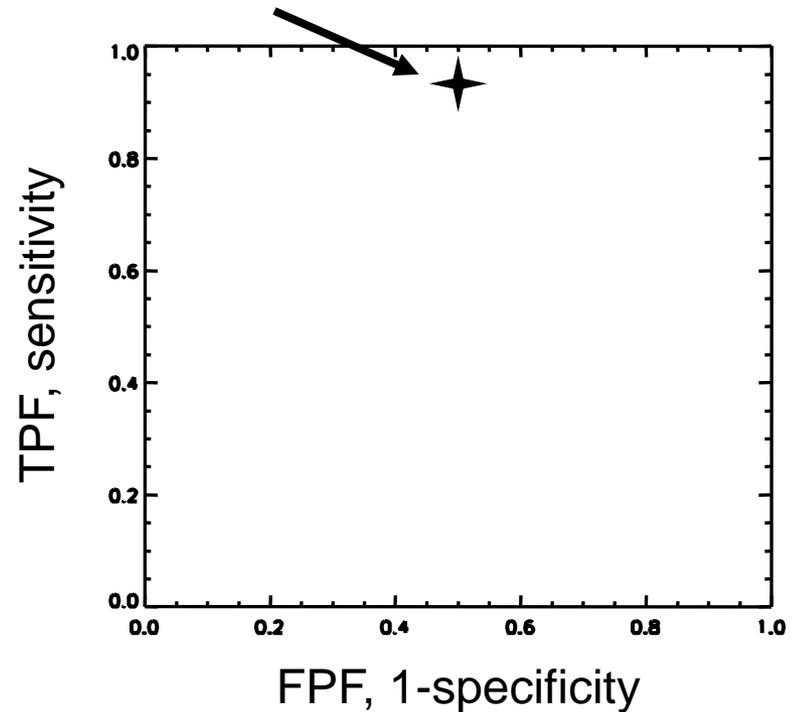


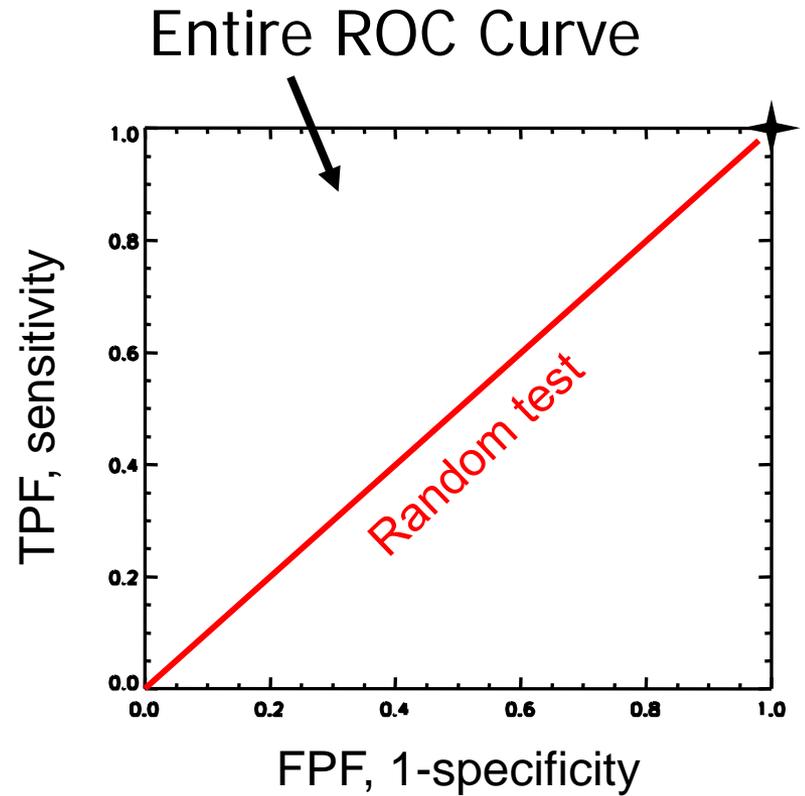
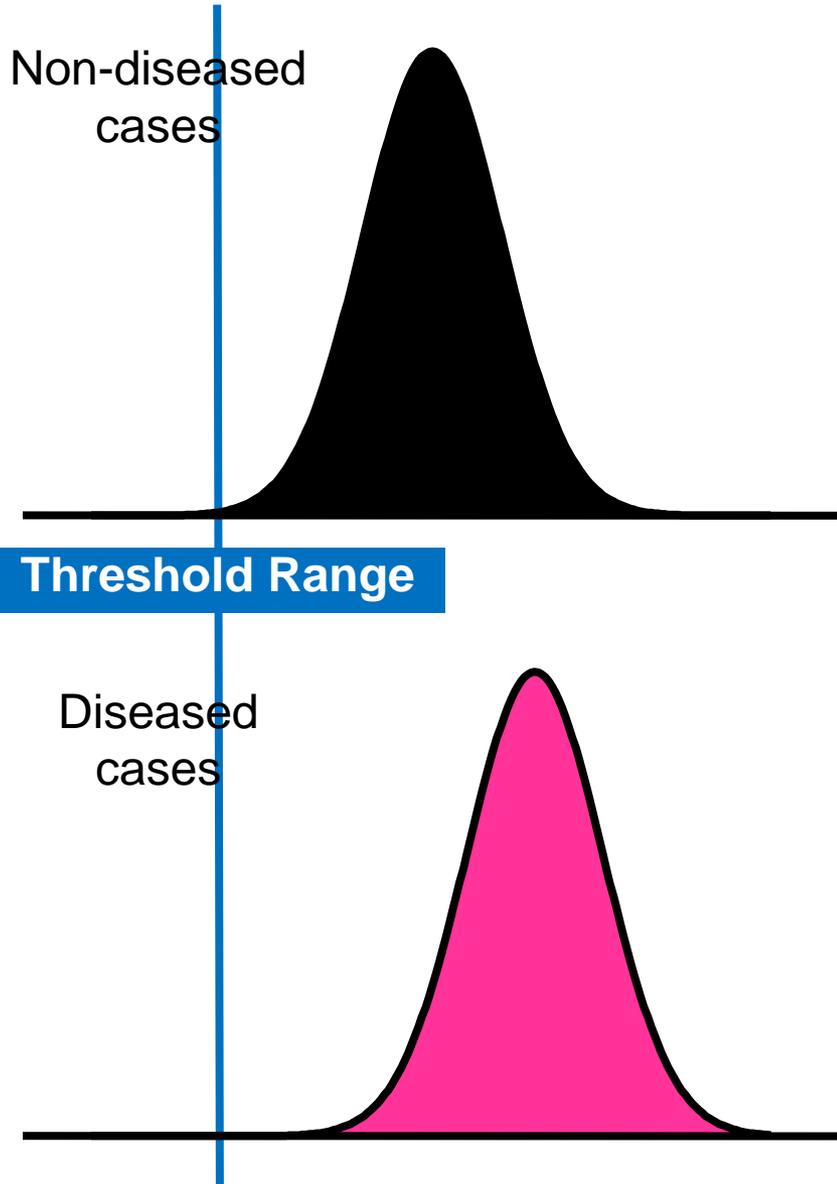
Single Operating Point



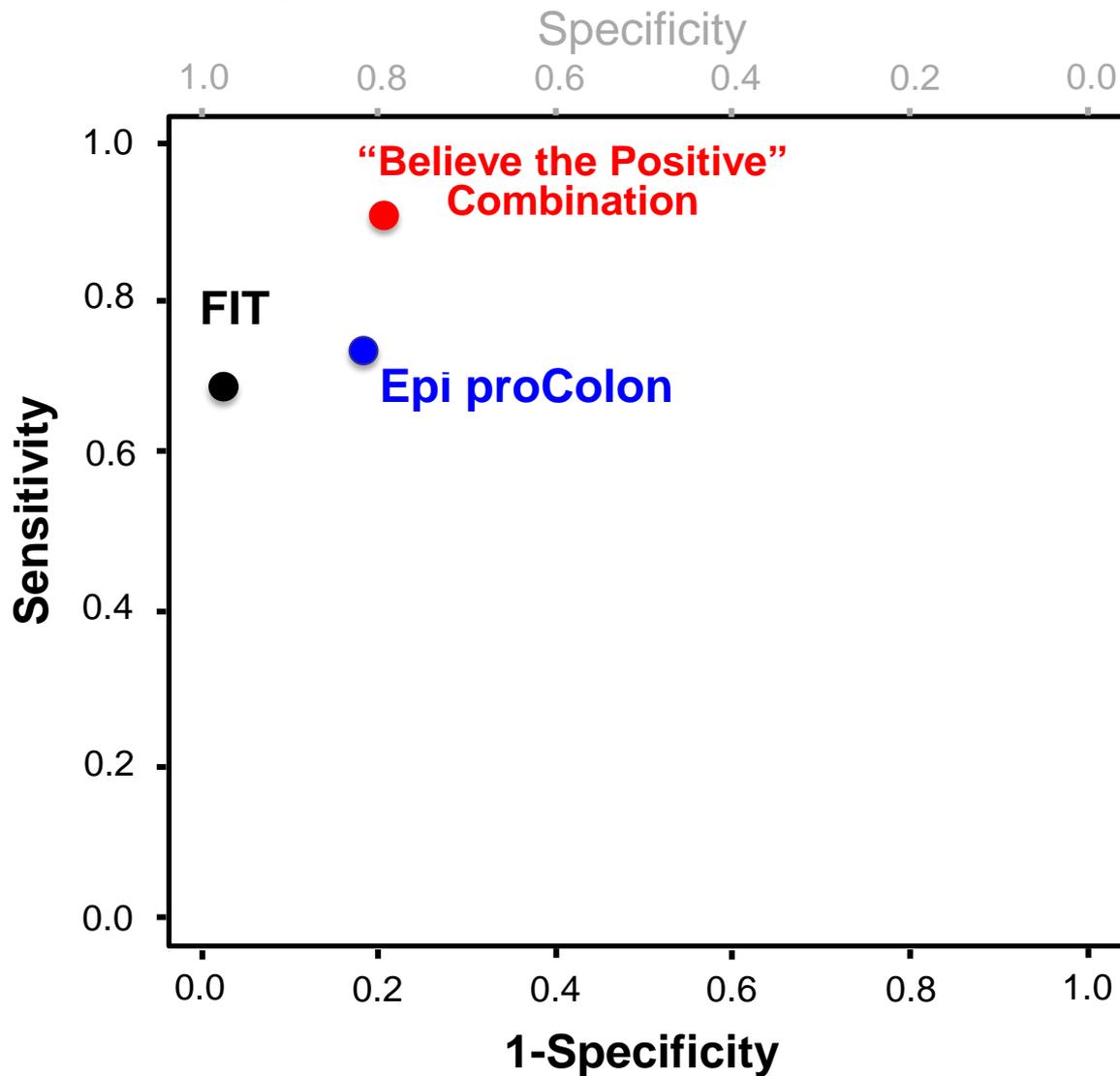


Single Operating Point

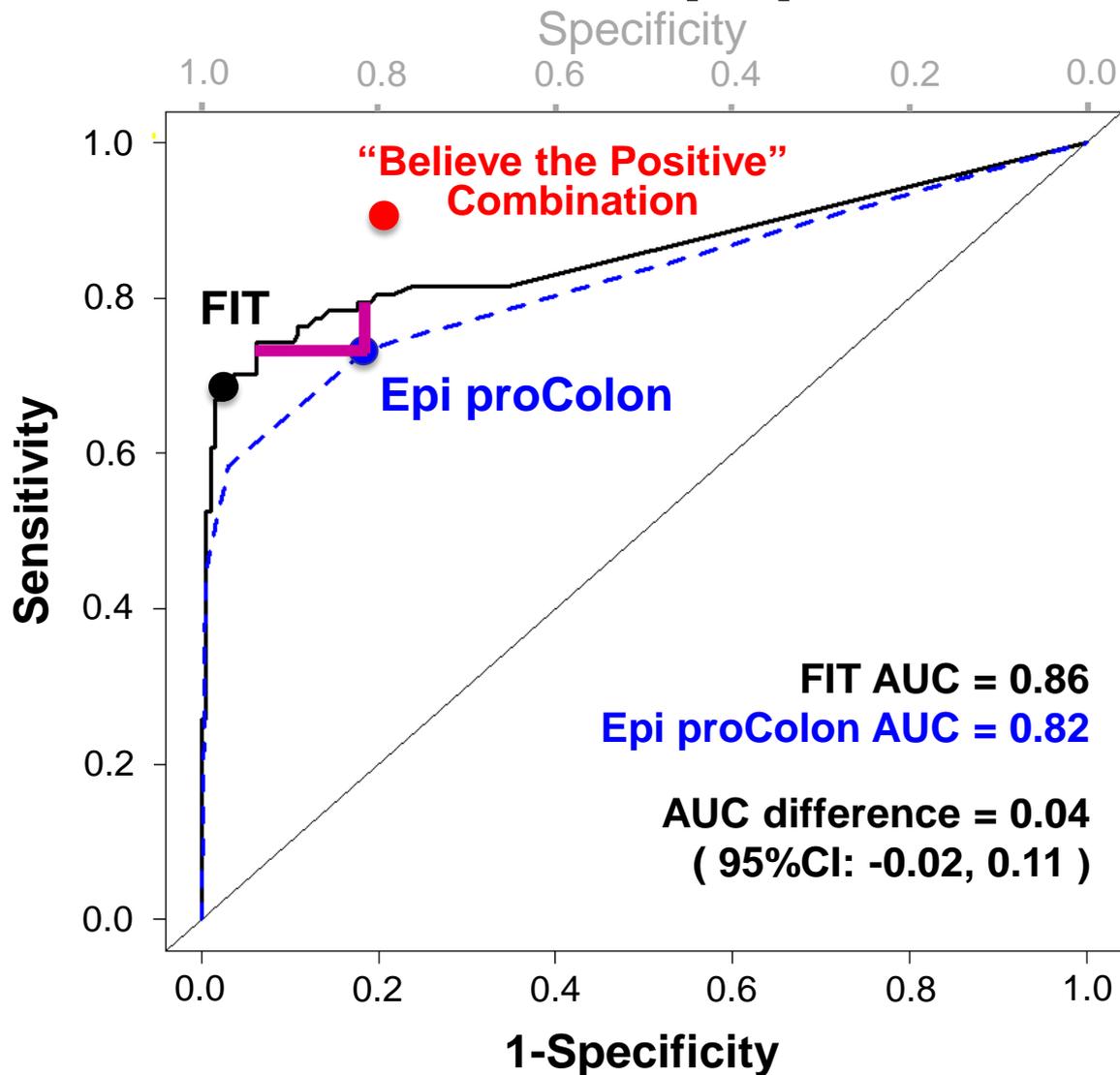




Operating Points: FIT vs Epi proColon



ROC Plots: FIT vs Epi proColon (FDA)



Benefit-Risk: (FDA)

Projection to Screening Population

- Screening 100,000 subjects
- Assume prevalence: 0.7% (PRESEPT Study)

	700 CRC cases		99,300 non-CRC cases		False Positives per True Positive
	True Positive	False Negative	False Positive	True Negative	
Epi proColon	505	195	19,037	80,263	37.7
FIT	476	224	2,573	96,727	5.4
Difference	29	-29	16,464	-16,464	
Difference ÷ 29	1	-1	571	-571	

Benefit-Risk: (FDA)

Projection to Screening Population

- Screening 100,000 subjects
- Assume prevalence: 0.7% (PRESEPT Study)

	700 CRC cases		99,300 non-CRC cases	
	True Positive	False Negative	False Positive	Adverse Events**
Epi proColon	505	195	19,037	130
FIT	476	224	2,573	18
Difference	29	-29	16,464	112
Difference ÷ 29	1	-1	571	4

Adverse event from follow-up colonoscopy after a false positive result

** Assume 0.68% risk of an adverse event from follow-up colonoscopy (Rutter CM, 2012)

Supplemental Study Summary

- Non-inferiority goal for sensitivity **was met**
- Non-inferiority goal for specificity **was not met**
- Lower specificity for Epi proColon, compared to FIT, may lead to increase in follow-up colonoscopies and associated adverse events
- Comparison Epi proColon to “Believe the Positive”:
 - Sensitivity increased with combination (statistical significance)
 - Specificity decreased with combination (statistical significance)
 - PPV increased with combination (no statistical significance)
 - NPV increased with combination (statistical significance)

Results Summary (Pivotal & Supplemental)

	Pivotal Epi proColon		Supplemental Epi proColon		Supplemental FIT	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
USA	57.7	78.6	72.2	80.8	68.0	97.4
Germany	83.3	79.8	--	--	--	--
Overall	68.2	78.8	72.2	80.8	68.0	97.4
Believe the positive	Sensitivity		88.7			
	Specificity		78.8			

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Review Considerations

- Discussion Question 1 → Test Performance
 - FIT comparison
 - CRC Screening Participation
- Discussion Question 2 → Role of Demographics
- Discussion Question 3 → Appropriate Scope of Claims, Follow-up
 - Test Independence
- Discussion Question 4 → Longitudinal Study Design

Average Risk, Noninvasive Screening

- Not applicable for heightened clinical concern
 - high risk patients (e.g., genetics)
 - diagnostic colonoscopy (e.g., symptoms)
 - surveillance colonoscopy (e.g., history of polyps)
- Noninvasive sample for screening
- Balance of prompting vs. avoiding invasive follow-up evaluation

FIT Comparison

- FIT recommended in different guidelines
- Range of reported FIT performance
- Advise direct head-to-head comparison to a FIT with well-documented CRC screening experience in intended use setting
- Supplemental clinical study differs from intended use setting with Group A collection post-colonoscopy and curative biopsy exclusion

Points for Discussion Question 1

- Studies in average risk screening (first time in pivotal study) colonoscopy patients
- Lower specificity (80.8%) compared to FIT (97.4%); 75% agreement in healthy donor pool
- Potential increase in avoidable colonoscopies, adverse events
- Epi proColon positivity for advanced adenoma (22%) and no evidence of disease (22%)
- Appropriate Intended Use, Cautions, Other?

CRC Screening Participation

- According to CDC, about one-third of average risk population unscreened; organized population-based efforts may be helpful
- A study with patients of average risk agreeing to screening colonoscopy does not address
 - Initial participation in screening by patients who would decline screening colonoscopy
 - Adherence to diagnostic colonoscopy
 - Diagnostic yield

Sponsor's Proposed Limitation

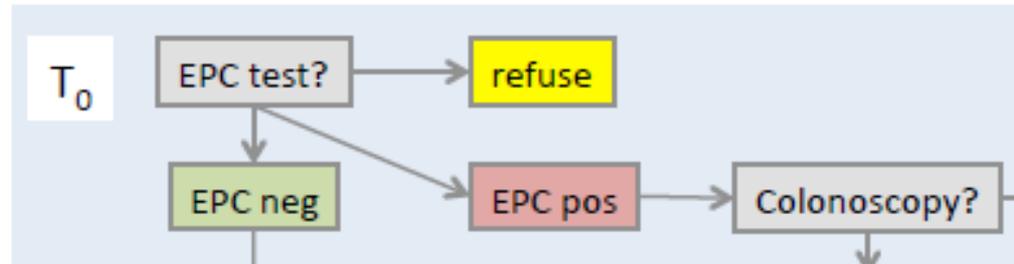
- “...unwilling, unable or do not undergo screening by other recommended screening methods”
 - Not evaluated in clinical studies
 - Adequate awareness and counseling regarding other methods
 - Appropriateness and importance of this consideration may not be apparent

Points for Discussion Question 2

- Caution for subgroup interpretation
- Differences in test performance associated with demographic factors (age, ethnicity)
 - e.g., specificity 68.8% for >75 years old
- Proposed limitation regarding varying CRC screening guideline recommendations for persons over age 75
- Appropriate labeling consideration

One-Time vs. Repeated

- Test Sensitivity, One-Time Testing, Cross-Sectional Study
- Screening Program Sensitivity, Repeated Testing, Longitudinal Study
- Interpret cross-sectional performance accordingly

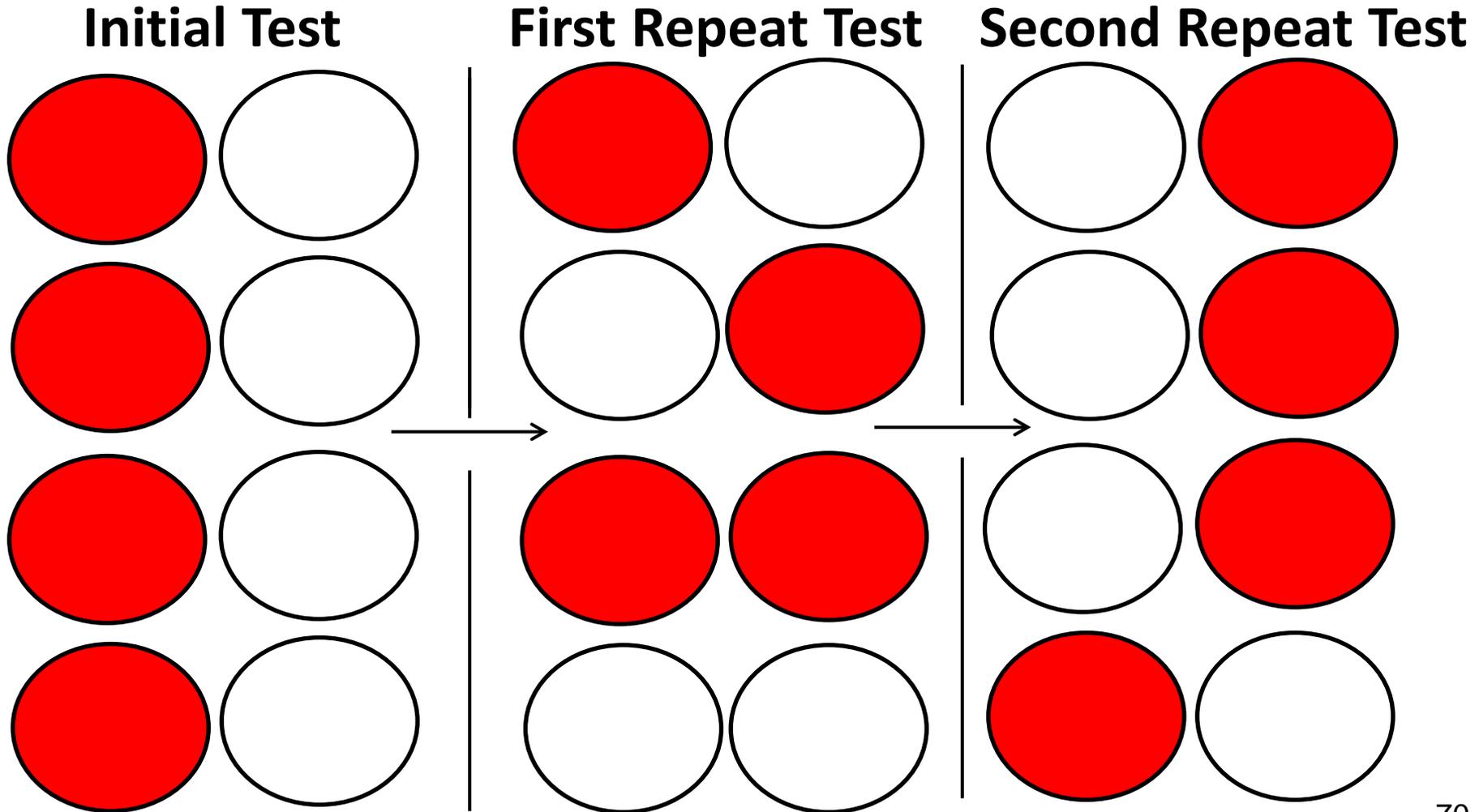


- Cross-sectional study provides performance for initial test
- What happens for patients who initially test negative?
- Performance for additional testing after initial negative test may be supported through longitudinal study

Independence of Test Results

- If Results Are Independent
 - e.g., multiple opportunities to detect a lesion with repeated use
- If Results Are Dependent
 - e.g., lesions are not and will not be detected by a particular test even with repeated use

Independent Test Scenario (1)

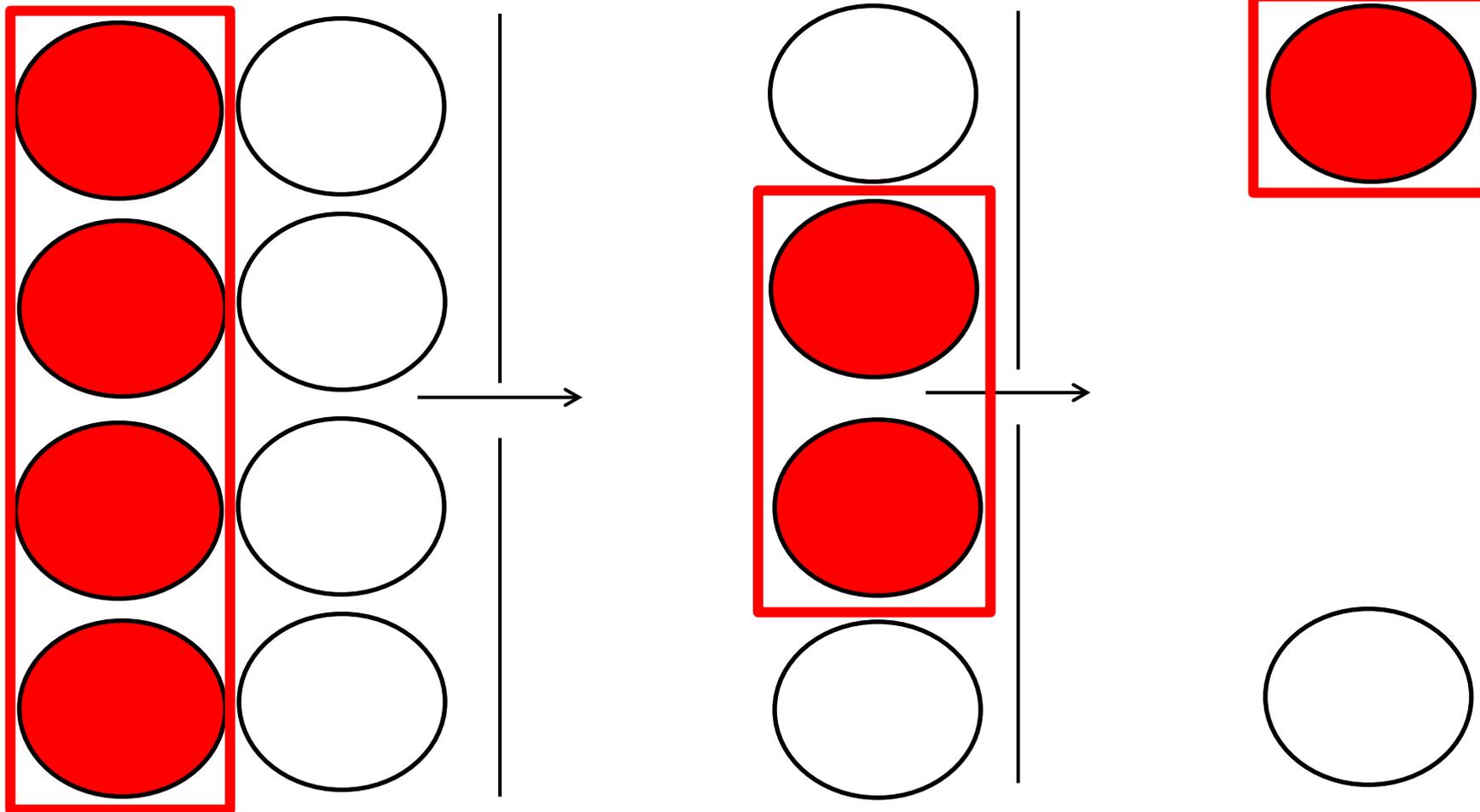


Independent Test Scenario (2)

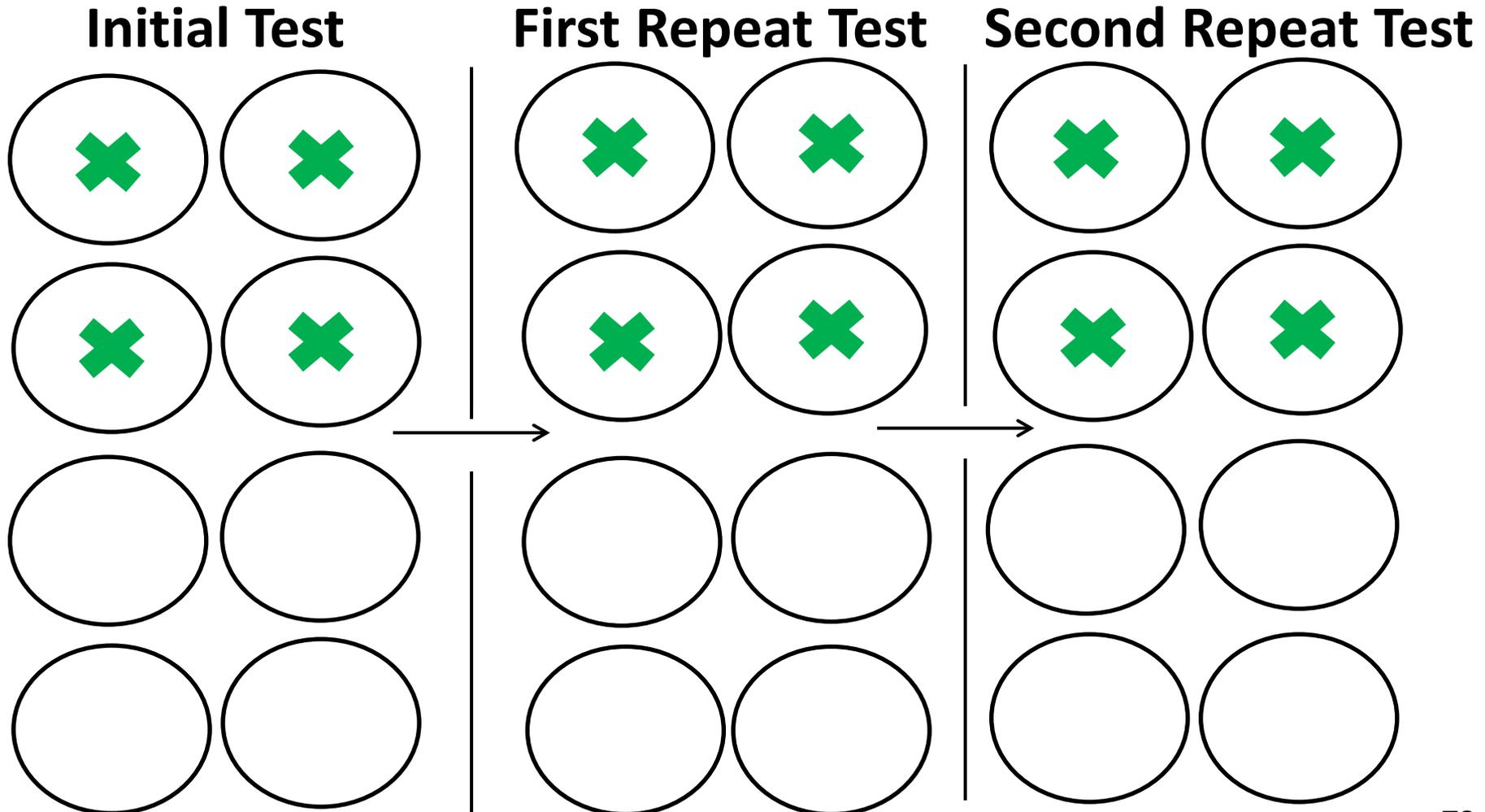
Initial Test

First Repeat Test

Second Repeat Test



Dependent Test Scenario (1)

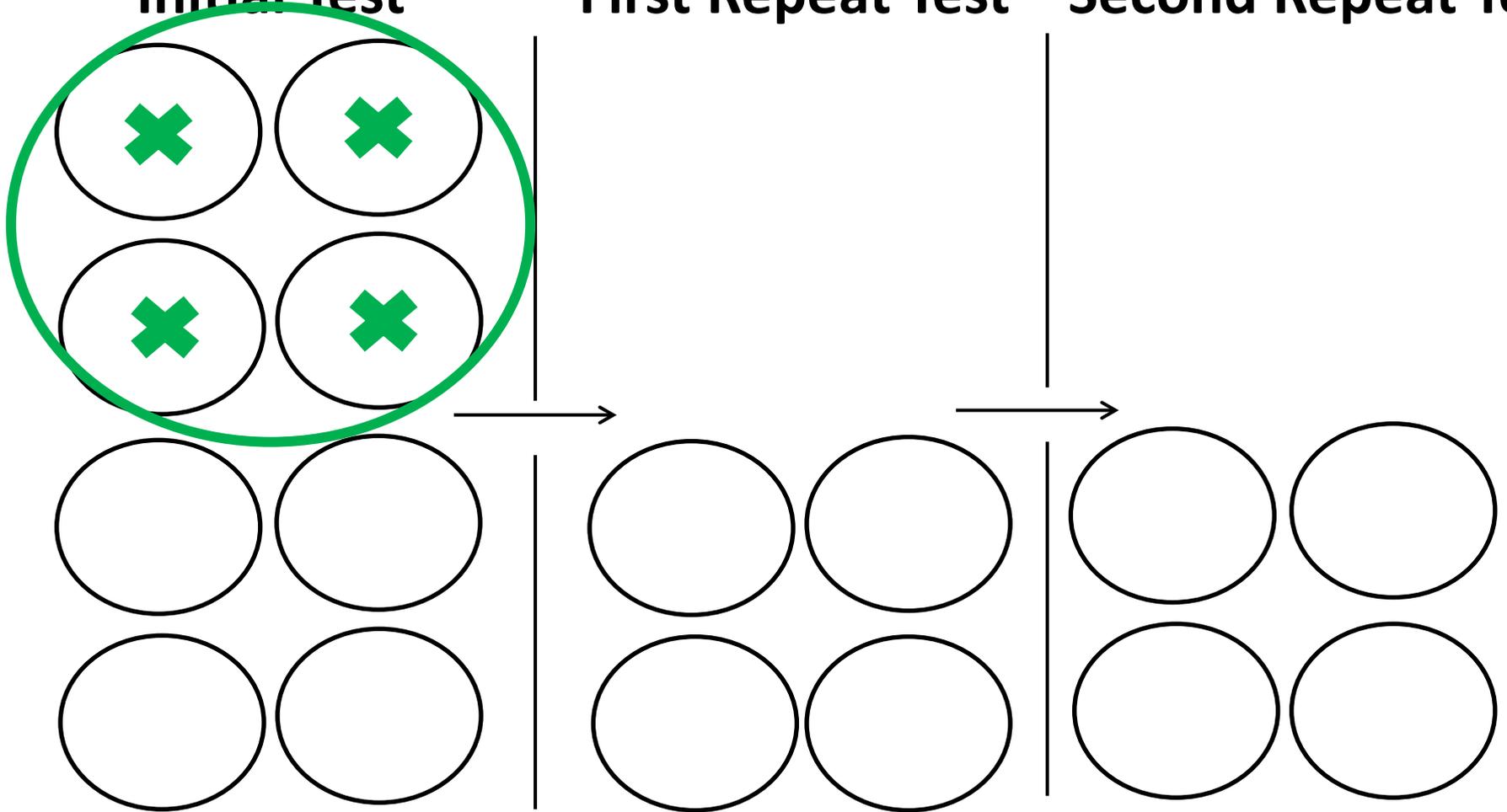


Dependent Test Scenario (2)

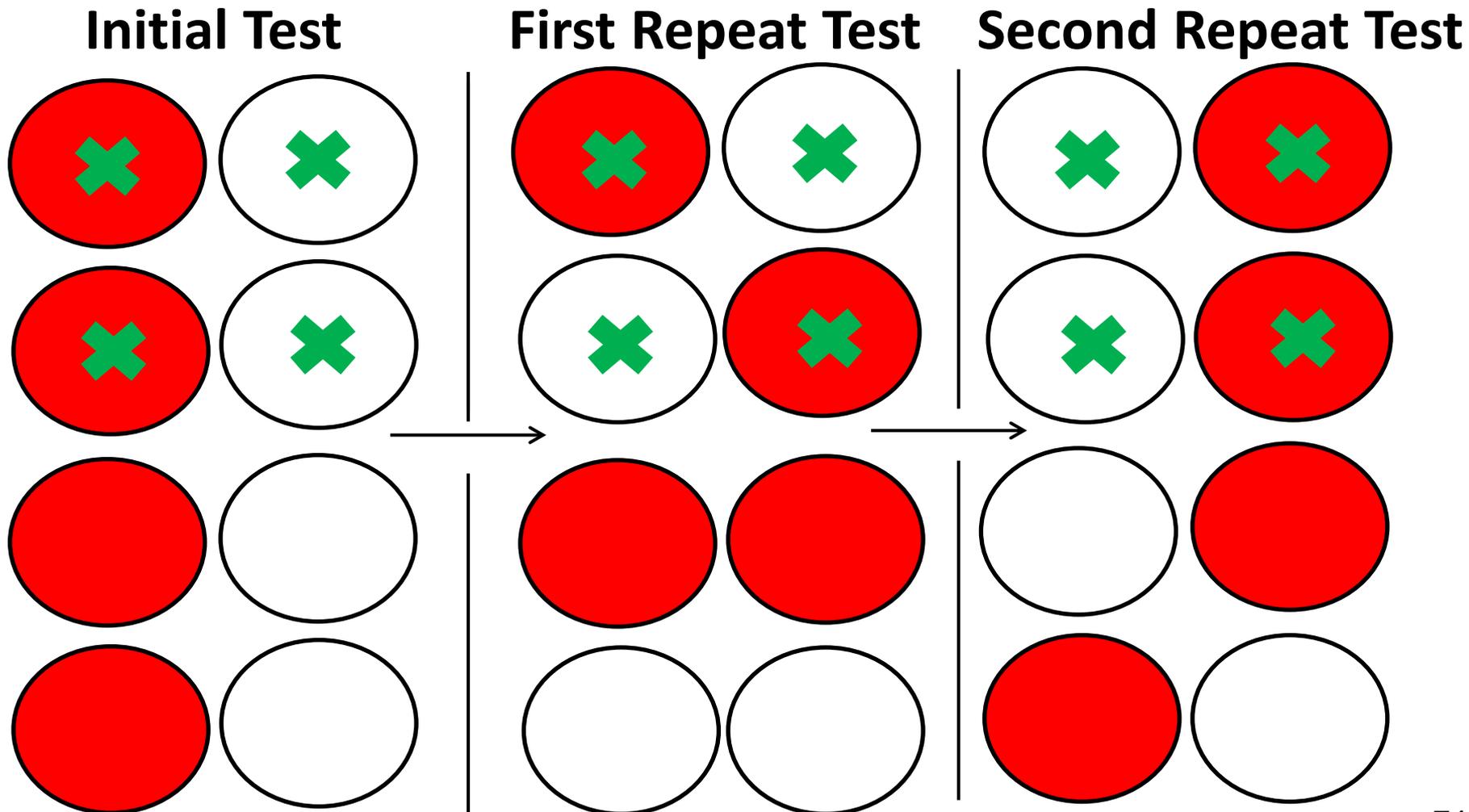
Initial Test

First Repeat Test

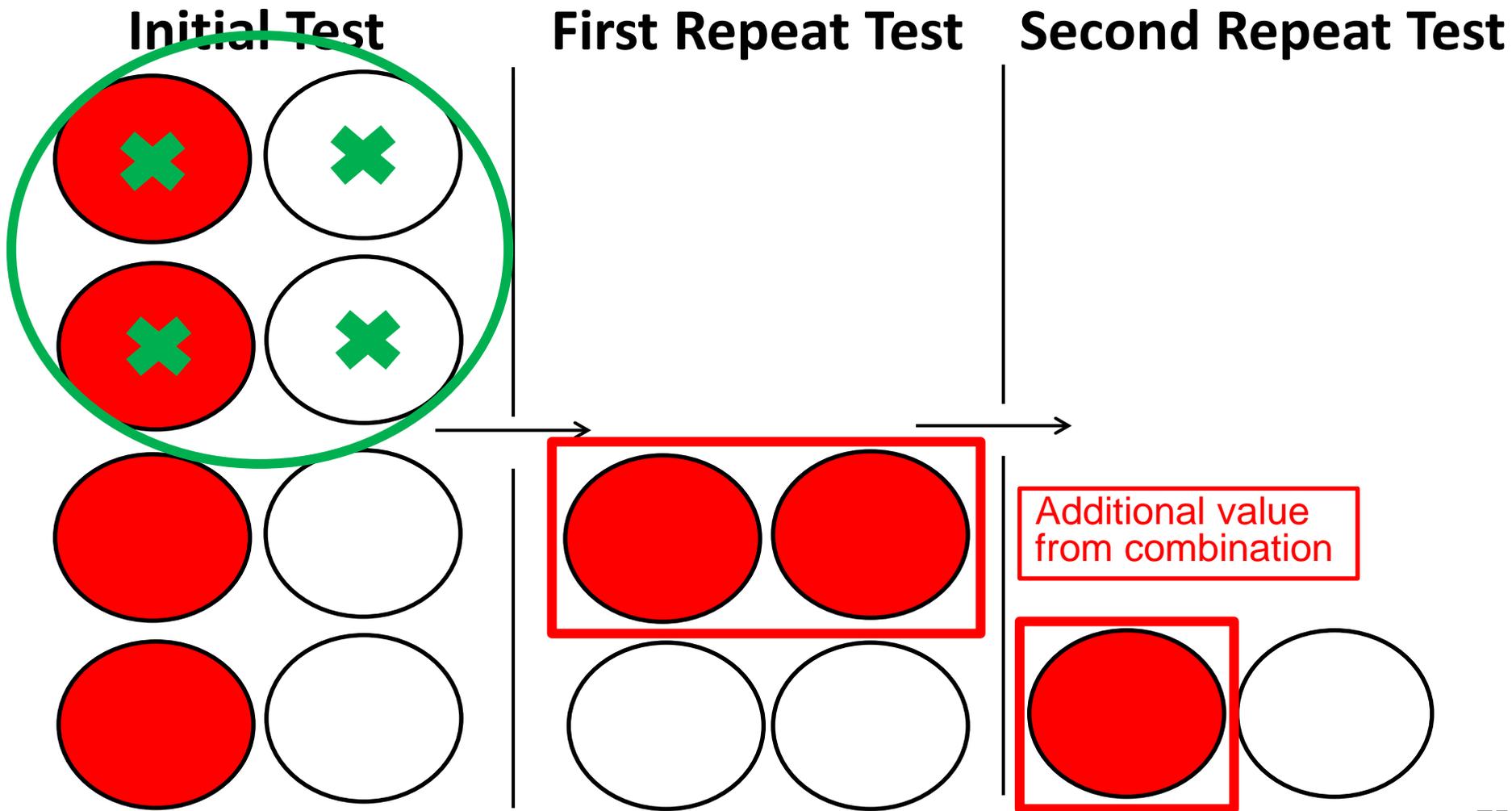
Second Repeat Test



Use Different Test for Follow-Up (1)



Use Different Test for Follow-Up (2)



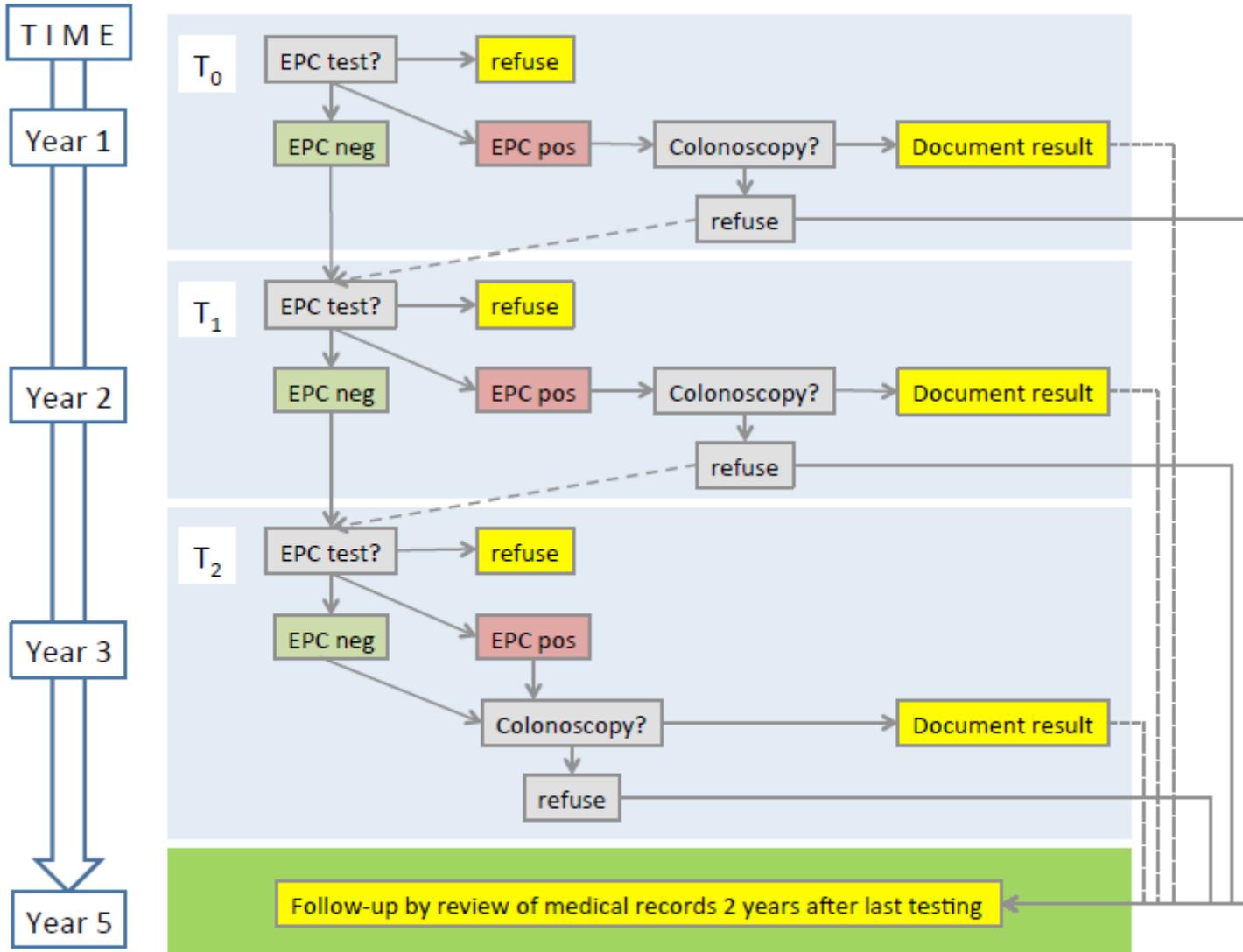
Points for Discussion Question 3 (1)

- Follow-up after testing for first time
- Diagnostic colonoscopy if positive
- Considerations if negative (e.g., time interval, testing method)
- Proposed interval of annual testing in sponsor's executive summary not clear in labeling
- Proposed warning: to continue participating in a colorectal cancer screening program

Points for Discussion Question 3 (2)

- Cross sectional study for one time, does not address repeat testing if a patient initially tests negative
- Proposed warning to continue participating in a colorectal cancer screening program
 - Scope of claims
 - Longitudinal study
 - Negative to positive conversion rate
 - Diagnostic yield
 - Predictive values

Proposed Study



Proposed Study Population

- Average risk population, according to the USPSTF recommendations for CRC screening;
- Representation of each gender, different age groups, and different ethnic backgrounds;
- No previous history of screening for CRC by colonoscopy;
- Subjects recruited from clinical sites utilizing Epi proColon.

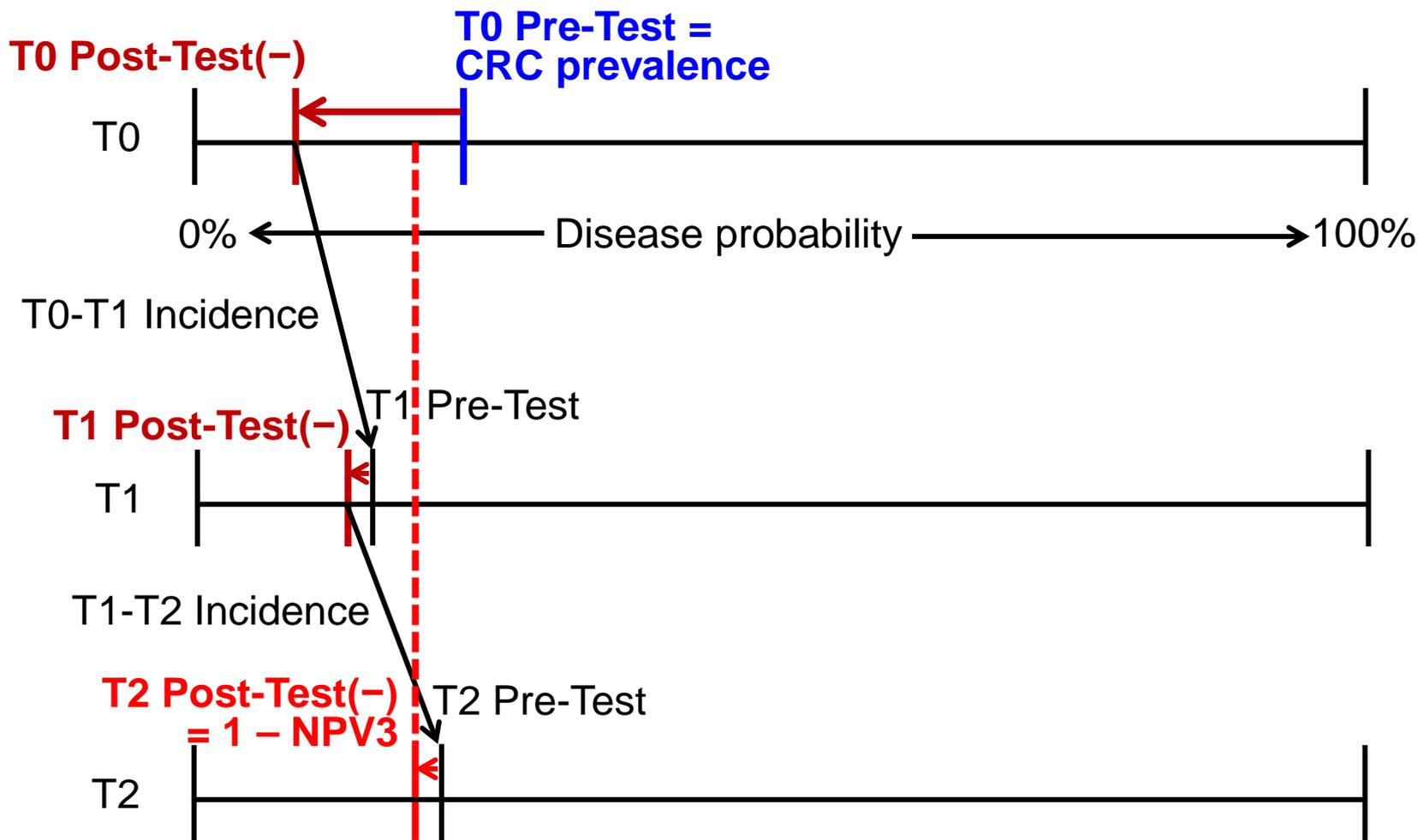
Proposed Study Hypothesis

- An annual screening program with Epi proColon significantly lowers the probability of carrying undetected CRC, such that NPV3 (i.e., the probability of not having CRC in individuals who test negative with annual Epi proColon testing for three years) $> 1 - \text{CRC prevalence}$, with statistical significance of $\alpha = 0.05$.

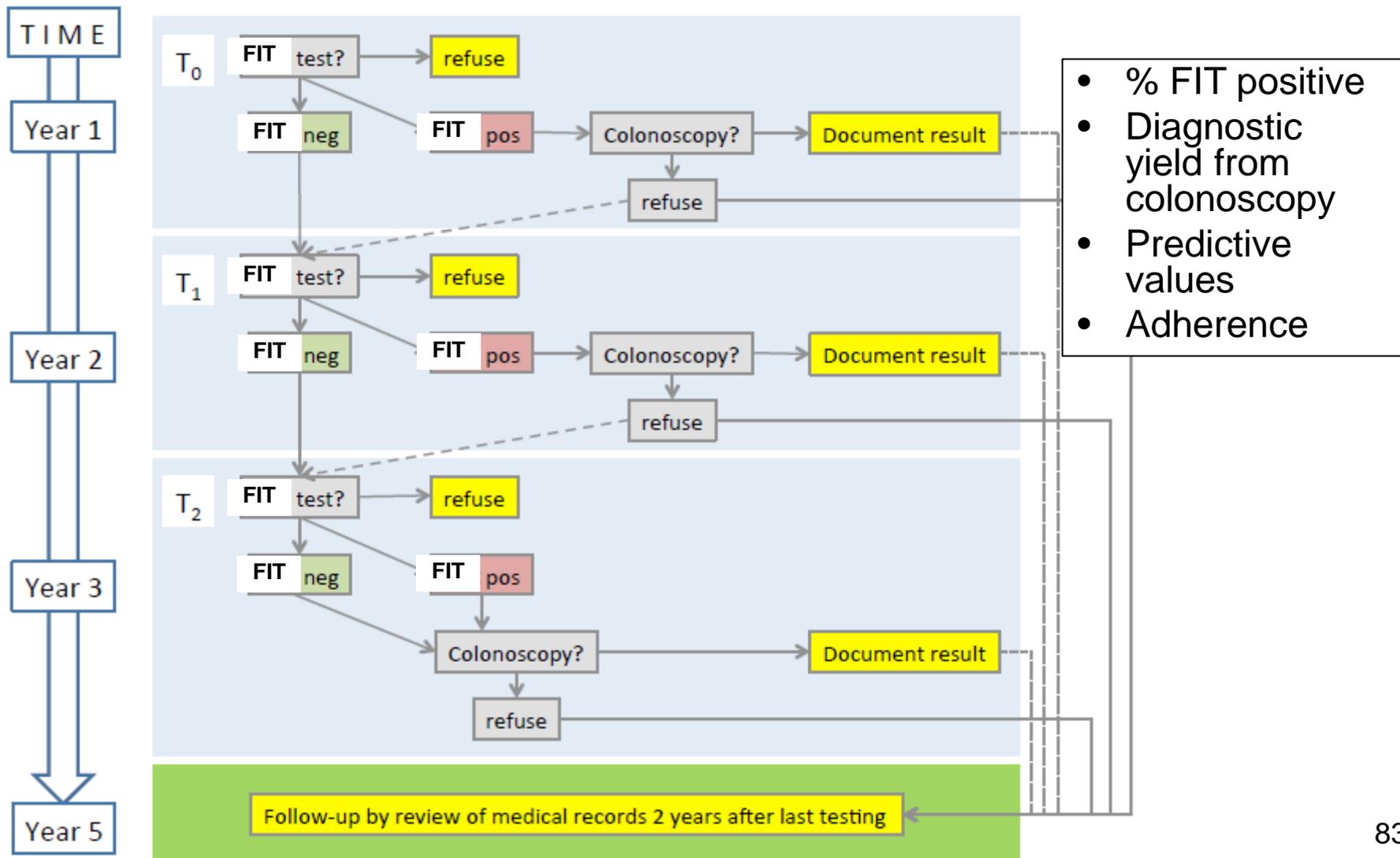
Points for Discussion Question 4

- Study population and conduct
 - Would forgo other screening options (e.g., annual FIT)
- Statistically and clinically meaningful performance evaluation
 - Comparison to other approaches (e.g., annual FIT)
 - Lower probability than prevalence after three negative tests could be achieved with limited value from repeat testing

1 - NPV3 < CRC Prevalence ?



Annual FIT Comparison?



Summary (1)

- Discussion Question 1 → Test Performance
 - Use for general average risk population
 - Lower specificity than FIT
 - Similar positivity in AA, no evidence of disease
 - Healthy donor pool inconsistently negative
 - Use for those not participating in screening
 - Not evaluated in clinical studies
 - Appropriate awareness and counseling for screening choice
- Discussion Question 2 → Role of Demographics
 - e.g., specificity decreases with age

Summary (2)

- Discussion Question 3 → Appropriate Scope of Claims, Follow-up
 - No information on repeat testing including independence of results
- Discussion Question 4 → Longitudinal Study Design
 - Meaningful performance
 - Comparison to accepted screening option



THANK YOU

Questions?