Shield is a Blood Based Colorectal Cancer Screening Test for Average-Risk Adults

May 23, 2024

Molecular and Clinical Genetics Panel

Guardant Health

Introduction

AmirAli Talasaz, PhD

Co-Chief Executive Officer

Guardant Health

Colorectal Cancer (CRC) Screening Saves Lives but Millions of Eligible Adults Are Not Screened

- CRC is 2nd leading cause of cancer-related death in US[1]
- Early detection improves survival and reduces preventable CRC deaths[2,3]
- Detection requires adherence to CRC screening test[4,5]
- Despite current screening modalities, screening rates remain below guideline recommended target[6,7]

New choices are needed to improve CRC screening

1. Siegel, 2024; 2. Wolf, 2018; 3. https://seer.cancer.gov/statfacts/html/colorect.html; 4. Roselló, 2019; 5. Doubeni, 2019;
6. Siegel, 2023; 7. https://www.cdc.gov/cancer/colorectal/statistics/use-screening-tests-BRFSS.htm

Current CRC Screening Landscape

Primary Screening Options

Visualization

Colonoscopy

Prioritized option

- Invasive procedure
- Can prevent cancer by removing polyps (or abnormal growth) during test[1]

Stool-Based

mt-sDNA

FIT

HSgFOBT

- Non-invasive

Second-Line

mSEPT9

- Poor device performance
  - 68% CRC sensitivity
  - 79% AN specificity
- Required patients decline primary screening tests
- ***No longer commercially available***

1. National Colorectal Cancer Roundtable Manual for Primary Care Practices, 2022

mt-sDNA = multitarget stool DNA; FIT = Fecal immunochemical test; HSgFOBT = high sensitivity guaiac fecal occult blood test

Shield Would Add Effective Blood-Based Screening Option to Be Offered Alongside Stool-Based Tests

Primary Screening Options

Colonoscopy

Prioritized option

- Invasive procedure
- Can prevent cancer by removing polyps (or abnormal growth) during test[1]

Stool-Based

mt-sDNA

FIT

HSgFOBT

- Non-invasive

Blood-Based

Shield

- Non-invasive
- Device performance in range of stool-based screening options

1. National Colorectal Cancer Roundtable Manual for Primary Care Practices, 2022

mt-sDNA = multitarget stool DNA; FIT = Fecal immunochemical test; HSgFOBT = high sensitivity guaiac fecal occult blood test

The NEW ENGLAND JOURNAL of MEDICINE

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A Cell-free DNA Blood-Based Test for Colorectal Cancer Screening

Daniel C. Chung, M.D., Darrell M. Gray II, M.D., M.P.H., Harminder Singh, M.D., Rachel B. Issaka, M.D., M.A.S., Victoria M. Raymond, M.S., Craig Eagle, M.D., Sylvia Hu, Ph.D., Darya I. Chudova, Ph.D., AmirAli Talasaz, Ph.D., Joel K. Greenson, M.D., Frank A. Sinicrope, M.D., Samir Gupta, M.D., M.S.C.S., and William M. Grady, M.D.

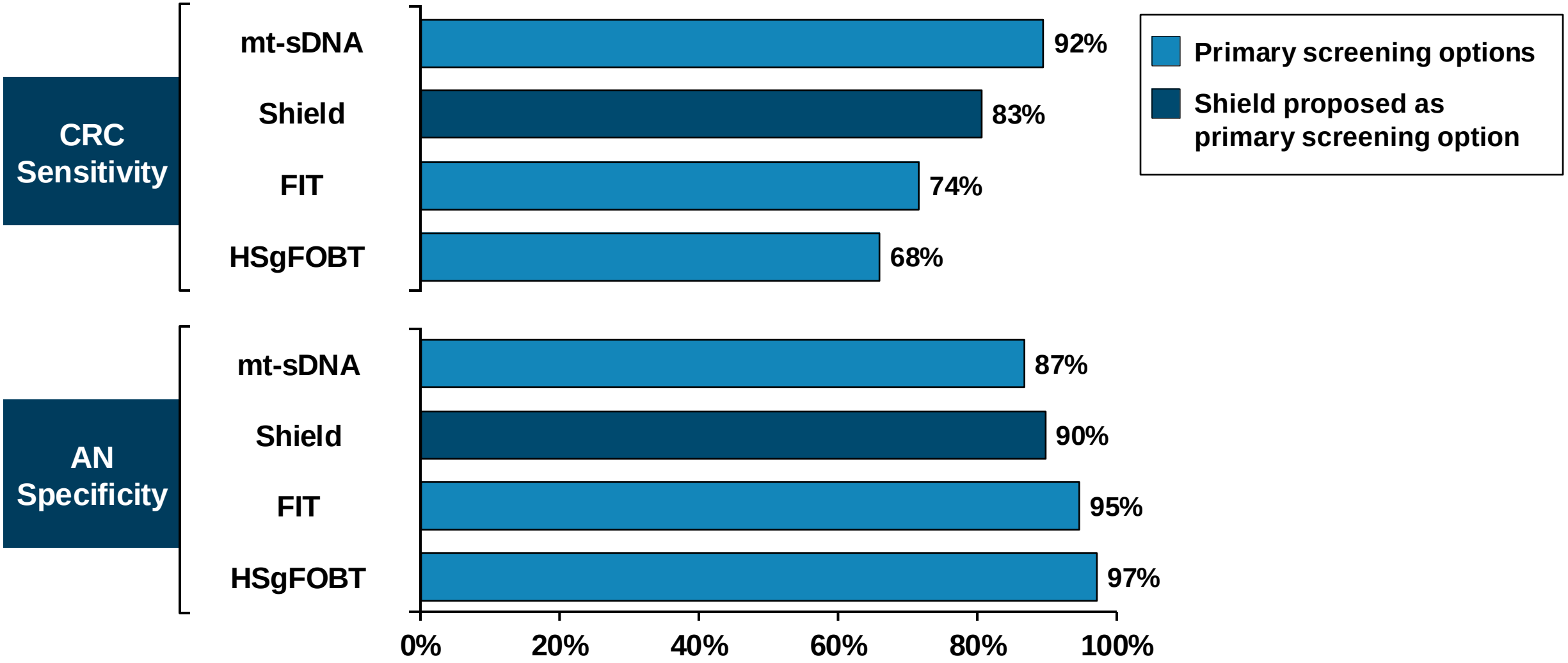
Performance Supports Shield as a CRC Screening Option

ECLIPSE[1]
Pivotal Study

CRC Sensitivity	**83.1%** (CI 72.2, 90.3)
AN Specificity	**89.6%** (CI 88.8, 90.3)

1. Chung, 2024; CI = Confidence Interval; AN = Advanced Neoplasia, defined as CRC or Advanced Adenoma

Shield Effectively Detects CRC, in Range with Non-Invasive CRC Screening Modalities



PMA P130017 FDA Summary of Safety and Effectiveness Data; Chung, 2024; Imperiale, 2014; Lin, 2021

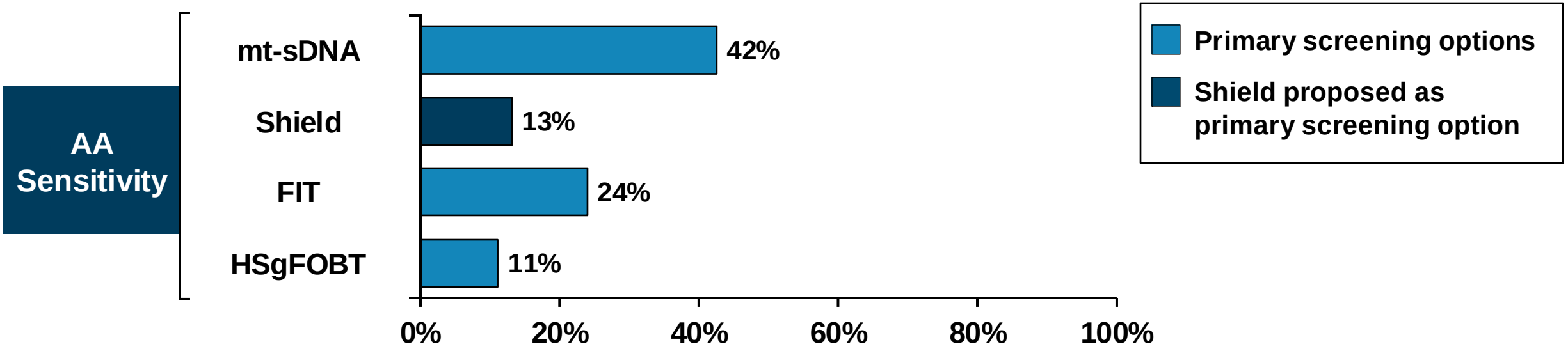
Shield is an Effective CRC Detection Device but Has Limited AA Sensitivity and Limited Prevention

ECLIPSE[1]
Pivotal Study

AA Sensitivity	**13.2%** (CI 11.3, 15.3)
High-Grade Dysplasia	**22.6%** (CI 11.4, 39.8)

1. Chung, 2024; AA = Advanced Adenoma

Shield's Advanced Adenoma Sensitivity on Lower End of Range of Stool-Based Tests



- Colonoscopy is the most accurate test for AA detection (up to 95%*)

Screening for AA is <u>not</u> a proposed Indication for Use of Shield

*≥ 10 mm adenomas

PMA P130017 FDA Summary of Safety and Effectiveness Data; Chung, 2024; Imperiale, 2014; Lin, 2021

Shield Proposed Intended Use and Indications for Use

The Shield test is a qualitative in vitro diagnostic test intended to **detect colorectal cancer** derived alterations in cell-free DNA from blood collected in the Guardant Shield Blood Collection Kit.

Shield is indicated for colorectal cancer screening in individuals at average risk of the disease, age 45 years or older.

- Patients with an “Abnormal Signal Detected” may have colorectal cancer or advanced adenoma and should be referred for colonoscopy evaluation.
- Shield is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals.

Shield Achieves Performance Established by Current Primary Stool-Based Screening Tests

	Current Primary Non-Invasive Stool CRC Tests			Blood Test
	mt-sDNA	FIT	HSgFOBT	Shield
CRC Sensitivity[1-5]	92%	67 – 74%	68%	83%
AN Specificity[1-5]	87%	95%	97%	90%
AA Sensitivity[1-5]	42%	23 – 24%	11%	13%
Adherence[4,6-22]	65 – 71%	28 – 68%	32 – 67%	88 – 99%

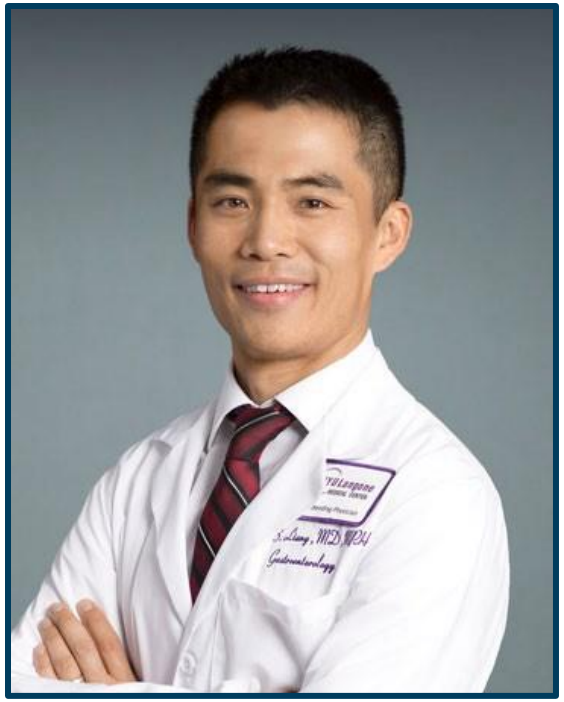
1. PMA P130017 FDA Summary of Safety and Effectiveness Data; 2. Imperiale, 2014; 3. Imperiale, 2024; 4. Lin, 2021; 5. Chung, 2024; 6. Quintero, 2012; 7. Jensen, 2016; 8. Oluloro, 2016; 9. Binefa, 2016; 10. Idigoras, 2017; 11. Bretagne, 2019; 12. Akram, 2017; 13. Singal, 2017; 14. Nielson, 2019; 15. Forsberg, 2022; 16. Conroy, 2018; 17. Weiser, 2020; 18. Miller-Wilson, 2021; 19. Inadomi, 2012; 20. Rose, 2024; 21. Raymond, 2023; 22. Liles, 2017

Agenda

Unmet Need	**Peter S. Liang, MD, MPH** Assistant Professor, Department of Medicine Assistant Professor, Department of Population Health NYU Grossman School of Medicine
Shield Development	**Darya Chudova, PhD** Chief Technology Officer Guardant Health
ECLIPSE Study Results	**Daniel Chung, MD** Medical Co-Director, Center for Cancer Risk Assessment Director, High-Risk GI Cancer Clinic Professor of Medicine, Harvard Medical School
Clinical Perspective	**Monnie Singleton, MD** CEO and Medical Director Singleton Health Center and Medical Center of Santee Orangeburg County, South Carolina
Conclusion	**Craig Eagle, MD** Chief Medical Officer Guardant Health

Additional Expert

Jason Connor, PhD
President & Lead Statistical Scientist
ConfluenceStat, LLC



Benefits of CRC Screening and Need for Additional Options

Peter S. Liang, MD, MPH

Assistant Professor, Department of Medicine

Assistant Professor, Department of Population Health

NYU Grossman School of Medicine

CRC is Major Public Health Concern in US

4th

Most diagnosed cancer[1]

2nd

Most common cause of cancer related death[1]

152,810

Estimated adults diagnosed with CRC in 2024[1]

53,010

Estimated deaths from CRC in 2024[1]

76%

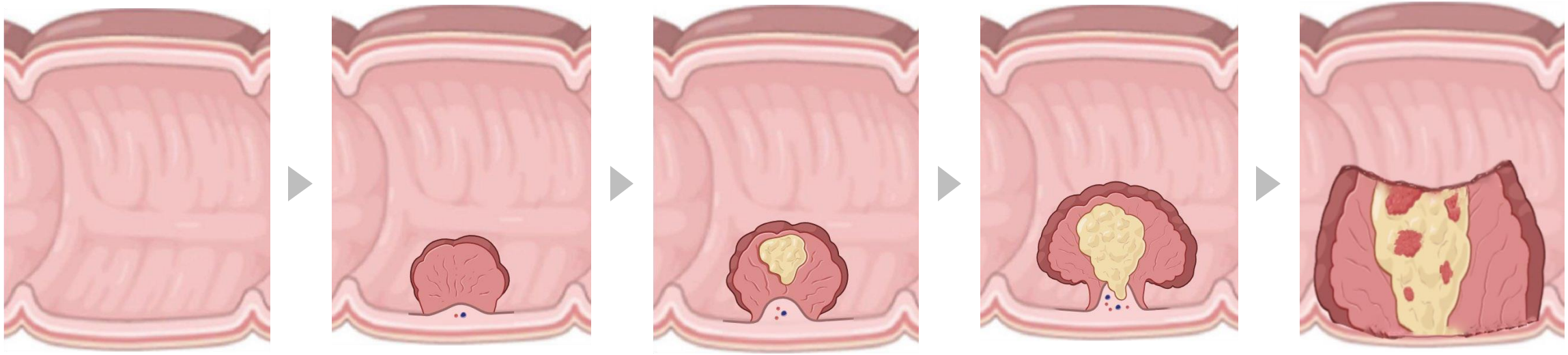
of CRC deaths occur in individuals not up to date with screening[2]

1. Siegel, 2024; 2. Doubeni, 2019

CRC is Well-Suited to Screening Due to Natural Progression of Disease

17 – 29 Years Total dwell time to CRC[1]

13 – 25 Years → **4 – 5 Years**



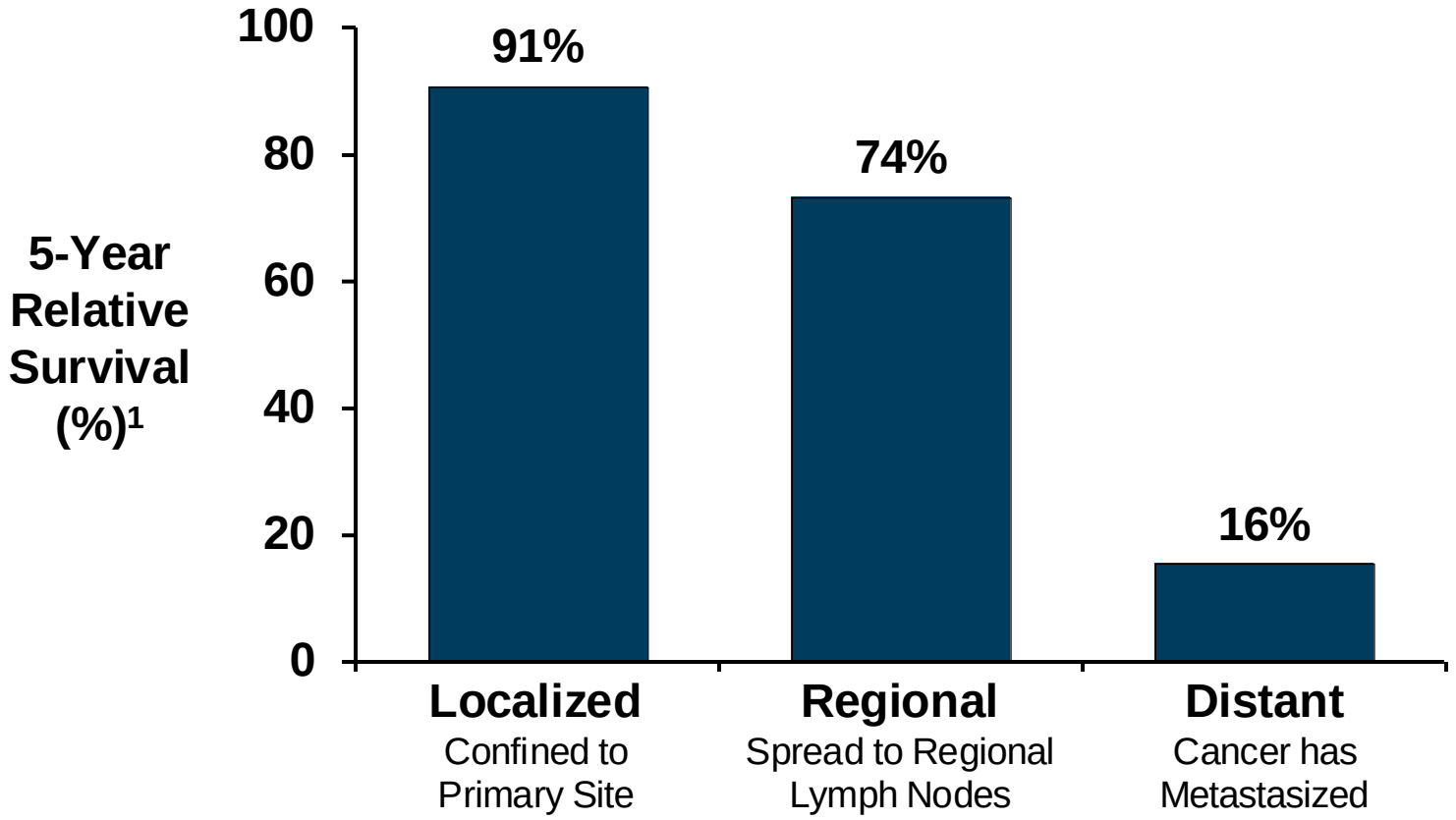
Normal | Adenomatous Polyp | Advanced Adenoma | Pre-Clinical Colorectal Cancer | Clinical Colorectal Cancer

1. Knudsen, 2021

Early CRC Detection Improves 5-Year Survival

National Cancer Institute, SEER Database (2014 – 2020)

Percent of Cases by Stage at Diagnosis[1]*	35%	36%	23%



Goal of CRC screening is to detect cancer as early as possible, to allow for early treatment

*Unknown stage at diagnosis = 6%

National Cancer Institute Colorectal Cancer Facts (people diagnosed with cancers of the colon between 2014 and 2020)

1. https://seer.cancer.gov/statfacts/html/colorect.html

USPSTF Guidelines Recommend CRC Screening for Adults Age 45 Years to 75 years[1]

	Visualization	Stool-Based		
Screening Options	**Colonoscopy**	**mt-sDNA**	**FIT**	**HSgFOBT**
Colorectal Cancer[1]	**Recommended**			
Population[1]	**Asymptomatic adults aged 45 – 75 at average risk of CRC**			
Benefits[1]	**Reduction in CRC mortality**			

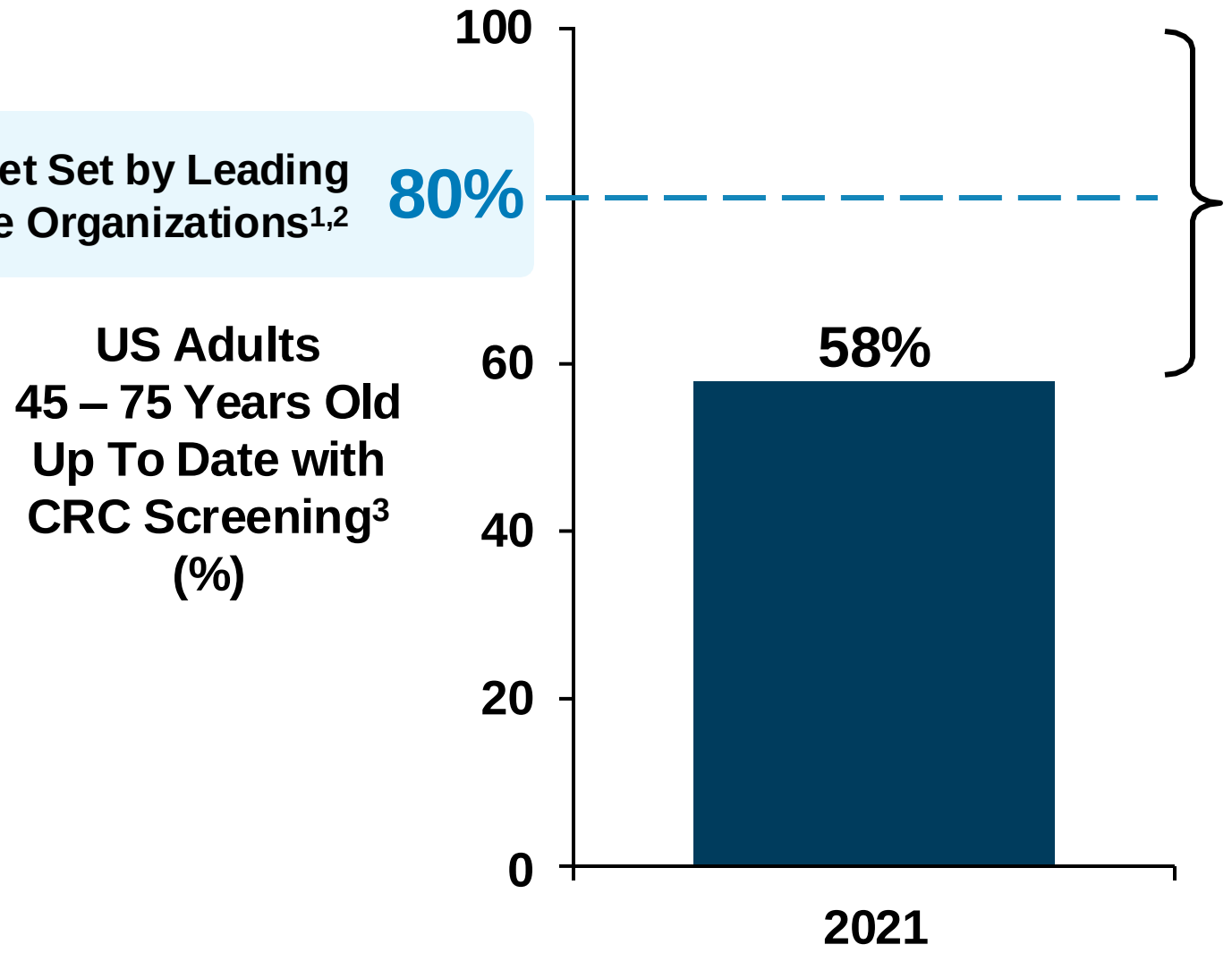
CRC screening is not a 'one size fits all' approach[1]

Clinicians and patients should be provided best evidence about various methods to enable informed, individual decision making

1. Lin, 2021

Despite Current Screening Options, Screening Rates Remain Below Guideline Recommended Target

Screening Target Set by Leading Healthcare Organizations[1,2] **80%**



~50 Million
US Adults
45 – 75 Years Old
Not Up To Date with
CRC Screening[4]

1. Meester, 2015; 2. Wender, 2020; 3. Siegel, 2023; 4. https://www.census.gov/library/visualizations/interactive/how-has-our-nations-population-changed.html

Current Non-Invasive Primary Screening Tests Effectively Detect CRC

	Primary Non-Invasive CRC Tests		
	mt-sDNA	FIT	HSgFOBT
CRC Sensitivity[1-4]	92%	67 – 74%	68%
AA Sensitivity[1-4]	42%	23 – 24%	11%

1. PMA P130017: FDA Summary of Safety and Effectiveness Data; 2. Imperiale, 2014; 3. Imperiale, 2024; 4. Lin, 2021

Adherence to Non-invasive Stool-Based Primary Screening Options Ranges from 28 – 71%

	Primary Non-Invasive CRC Tests		
	mt-sDNA	FIT	HSgFOBT
CRC Sensitivity[1-4]	92%	67 – 74%	68%
Adherence[4-18]	65 – 71%	28 – 68%	32 – 67%

- **Adherence**: Proportion of individuals offered a screening test and elected to complete the test
- Adherence to blood-based screening tests range from 88% – 99%[19-21]

1. PMA P130017 FDA Summary of Safety and Effectiveness Data; 2. Imperiale, 2014; 3. Imperiale, 2024; 4. Lin, 2021; 5. Quintero, 2012; 6. Jensen, 2016; 7. Oluloro, 2016; 8. Binefa, 2016; 9. Idigoras, 2017; 10. Bretagne, 2019; 11. Akram, 2017; 12. Singal, 2017; 13. Nielson, 2019; 14. Forsberg, 2022; 15. Conroy, 2018; 16. Weiser, 2020; 17. Miller-Wilson, 2021; 18. Inadomi, 2012; 19. Rose, 2024; 20. Raymond, 2023; 21. Liles, 2017

Standard of Care Screening Options Have Known Barriers Impacting Adherence

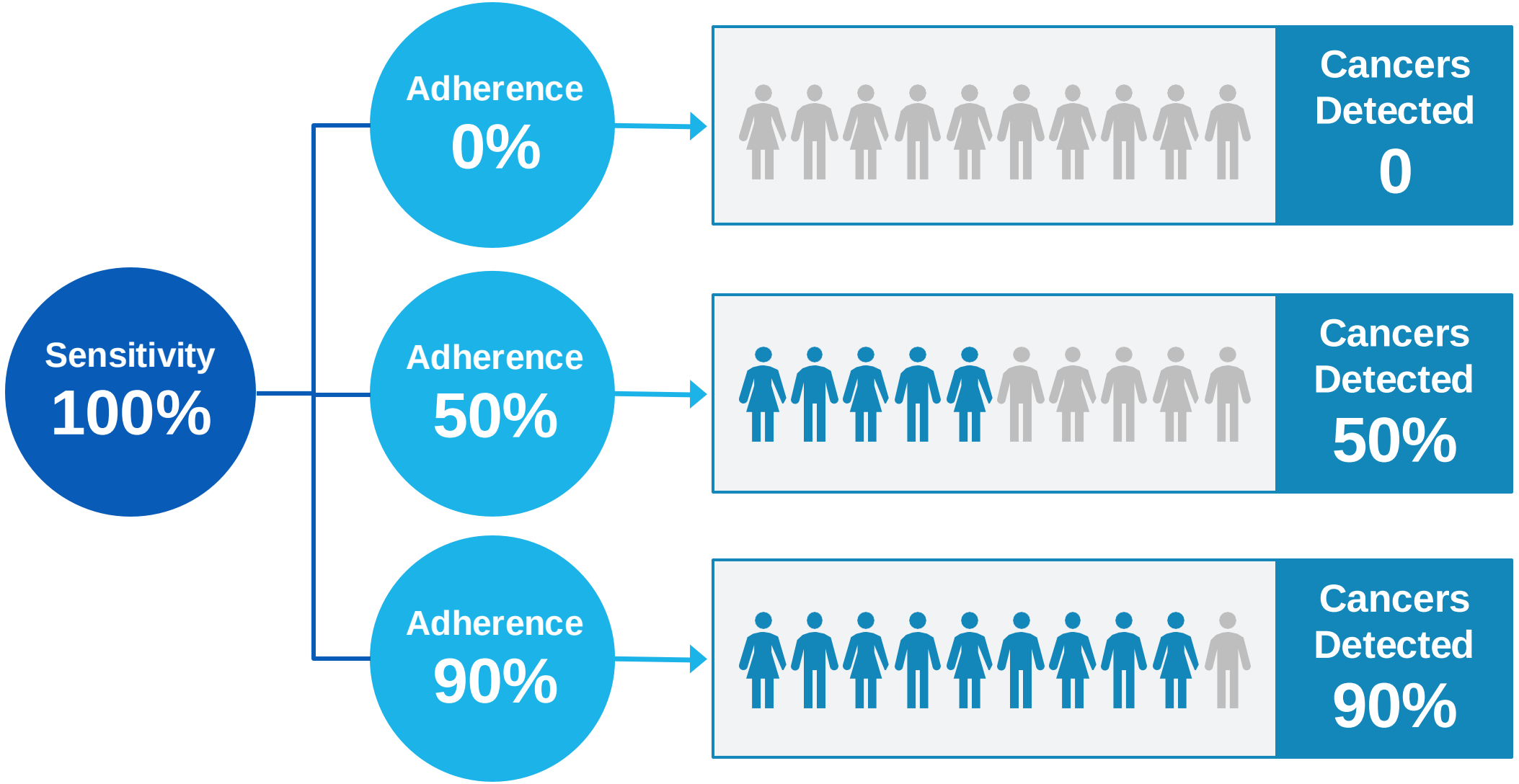
	Primary Non-Invasive CRC Tests		
	mt-sDNA	FIT	HSgFOBT
CRC Sensitivity[1-4]	92%	67 – 74%	68%
Adherence[4-18]	65 – 71%	28 – 68%	32 – 67%

Barriers[19-21]

- Aversion to handling stool
- Complex, multiple step process can be challenging for patients

1. PMA P130017 FDA Summary of Safety and Effectiveness Data; 2. Imperiale, 2014; 3. Imperiale, 2024; 4. Lin, 2021; 5. Quintero, 2012; 6. Jensen, 2016; 7. Oluloro, 2016; 8. Binefa, 2016; 9. Idigoras, 2017; 10. Bretagne, 2019; 11. Akram, 2017; 12. Singal, 2017; 13. Nielson, 2019; 14. Forsberg, 2022; 15. Conroy, 2018; 16. Weiser, 2020; 17. Miller-Wilson, 2021; 18. Inadomi, 2012; 19. Green, 2017; 20. Redwood, 2023; 21. Schneider, 2023

Sensitivity x Adherence = Detection



Adherence = Individuals who were offered the screening test, elected to complete the test

Impact of Adherence on Probability of CRC Detection with Current Screening Tests

	Primary Non-Invasive CRC Tests		
	mt-sDNA	FIT	HSgFOBT
CRC Sensitivity[1-4]	**92%**	**67 – 74%**	**68%**
Adherence[4-18]	**65 – 71%**	**28 – 68%**	**32 – 67%**
Estimated CRC Detection (CRC Sensitivity x Adherence)	**60 – 65%**	**19 – 50%**	**22 – 46%**

1. PMA P130017 FDA Summary of Safety and Effectiveness Data; 2. Imperiale, 2014; 3. Imperiale, 2024; 4. Lin, 2021; 5. Quintero, 2012; 6. Jensen, 2016; 7. Oluloro, 2016; 8. Binefa, 2016; 9. Idigoras, 2017; 10. Bretagne, 2019; 11. Akram, 2017; 12. Singal, 2017; 13. Nielson, 2019; 14. Forsberg, 2022; 15. Conroy, 2018; 16. Weiser, 2020; 17. Miller-Wilson, 2021; 18. Inadomi, 2012

CRC Screening Benefits Require Person to be Up-to-Date at Regular Intervals Over 3 Decades

	Primary Non-Invasive CRC Tests		
	mt-sDNA	FIT	HSgFOBT
CRC Sensitivity[1-4]	92%	67 – 74%	68%
Adherence[4-18]	65 – 71%	28 – 68%	32 – 67%
Screening Interval[4]	1-3 Years	1 Year	1 Year
Lifetime Tests*	11-31	31	31

*Lifetime based on CRC screening between ages of 45 to 75 years

1. PMA P130017 FDA Summary of Safety and Effectiveness Data; 2. Imperiale, 2014; 3. Imperiale, 2024; 4. Lin, 2021; 5. Quintero, 2012; 6. Jensen, 2016; 7. Oluloro, 2016; 8. Binefa, 2016; 9. Idigoras, 2017; 10. Bretagne, 2019; 11. Akram, 2017; 12. Singal, 2017; 13. Nielson, 2019; 14. Forsberg, 2022; 15. Conroy, 2018; 16. Weiser, 2020; 17. Miller-Wilson, 2021; 18. Inadomi, 2012

Summary of Unmet Need

- Despite available screening tests, ~50 million adults not up to date with CRC screening
- CRC is still 2nd leading cause of cancer-related death in US
- Patients and providers need additional CRC screening options that are convenient, noninvasive, and accurate
- Potential benefits of an effective blood-based screening option
  - Enhance patient access
  - Increase number of individuals up to date with screening
  - Reduce preventable CRC deaths

Shield Operating Principles and Device Development

Darya Chudova, PhD

Chief Technology Officer

Guardant Health

Cell-Free DNA (cfDNA) Fragments Originating from Tumor are Accessible in Circulation

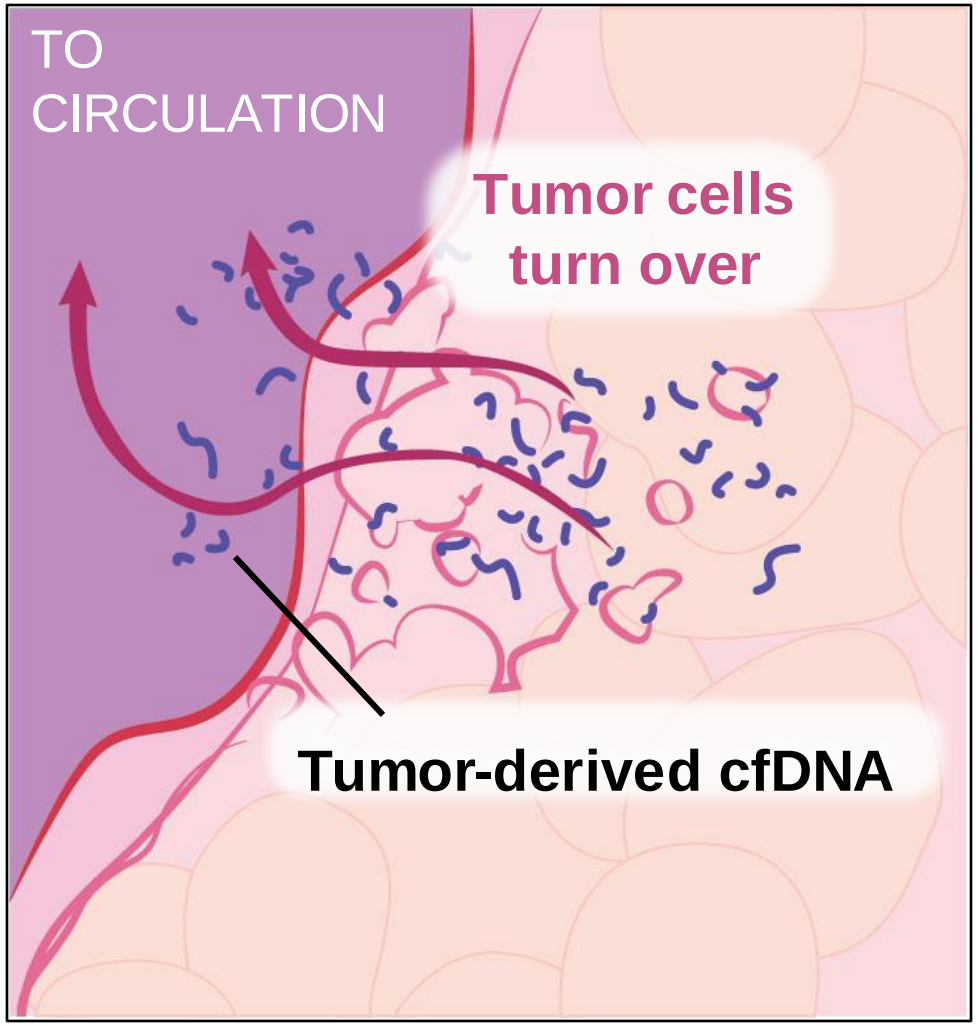
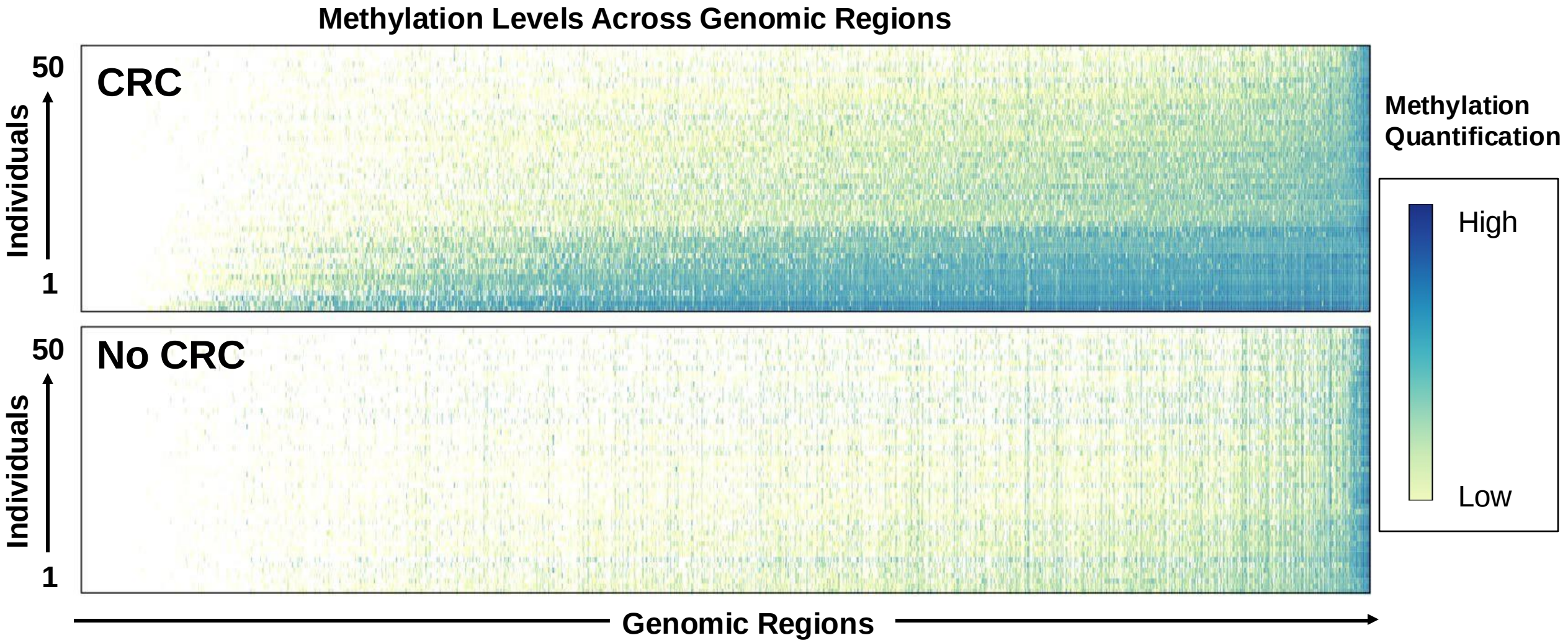


Figure adapted from Lo, 2024

- Cells shed DNA into circulation; digested into smaller fragments known as cfDNA
- Tumors contain significant number of genomic and epigenomic alterations
- Tumor derived cfDNA carries alterations into bloodstream

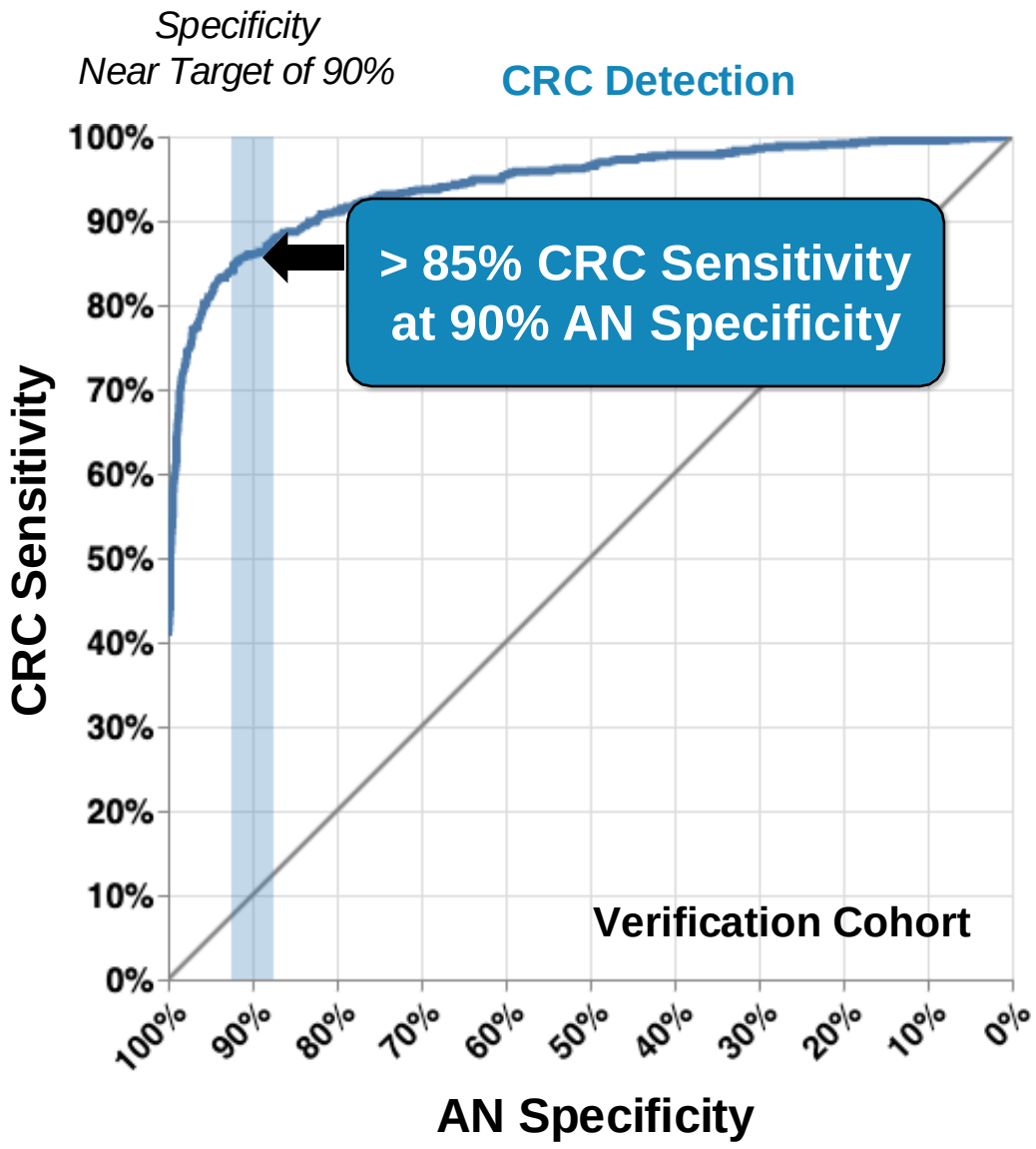
Guardant360 CDx test was the first comprehensive liquid biopsy test approved by the FDA

cfDNA Methylation Differentiates Individuals With and Without CRC



Shield Classification Model Developed and Verified Using Large Independent Development Cohorts

Assay Development	**cfDNA Analysis in Informative Regions**
Model Development	**1,470** CRC cases (all stages) **2,340** Cancer-free controls
Performance Verification (pre-pivotal)	**1,050** CRC cases (all stages) **710** Colonoscopy non-AN controls



AN = Advanced Neoplasia, defined as CRC or Advanced Adenoma

The details of classification development have not been fully reviewed by the FDA

Summary of Shield Device Development

- Shield relies on well-established principles of cfDNA carrying tumor-associated DNA alterations into circulation
- Strong CRC detection capability demonstrated using > 1,000 independent CRC cases in pre-pivotal verification
- Analytical studies involving > 15,000 sample test events achieved their pre-specified objectives

ECLIPSE Study Design, Effectiveness, and Safety Results

Daniel Chung, MD

Medical Co-Director, Center for Cancer Risk Assessment

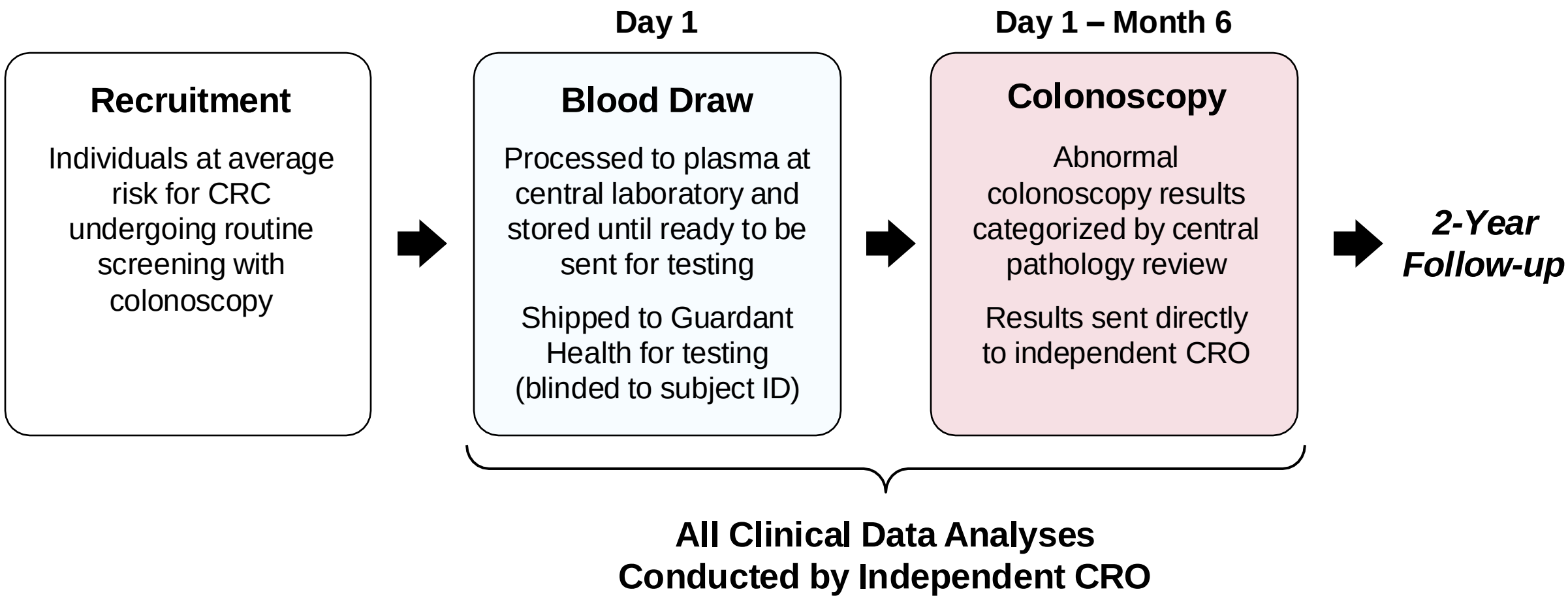
Director, High-Risk GI Cancer Clinic

Massachusetts General Hospital

Professor of Medicine, Harvard Medical School

ECLIPSE: Prospective, US Based, Multi-Center Study of Shield Performance to Detect CRC

- Study enrolled participants from October 2019 – September 2022



CRO = Clinical Research Organization

ECLIPSE Enrolled Participants at Average Risk for CRC and Undergoing Routine Screening with Colonoscopy

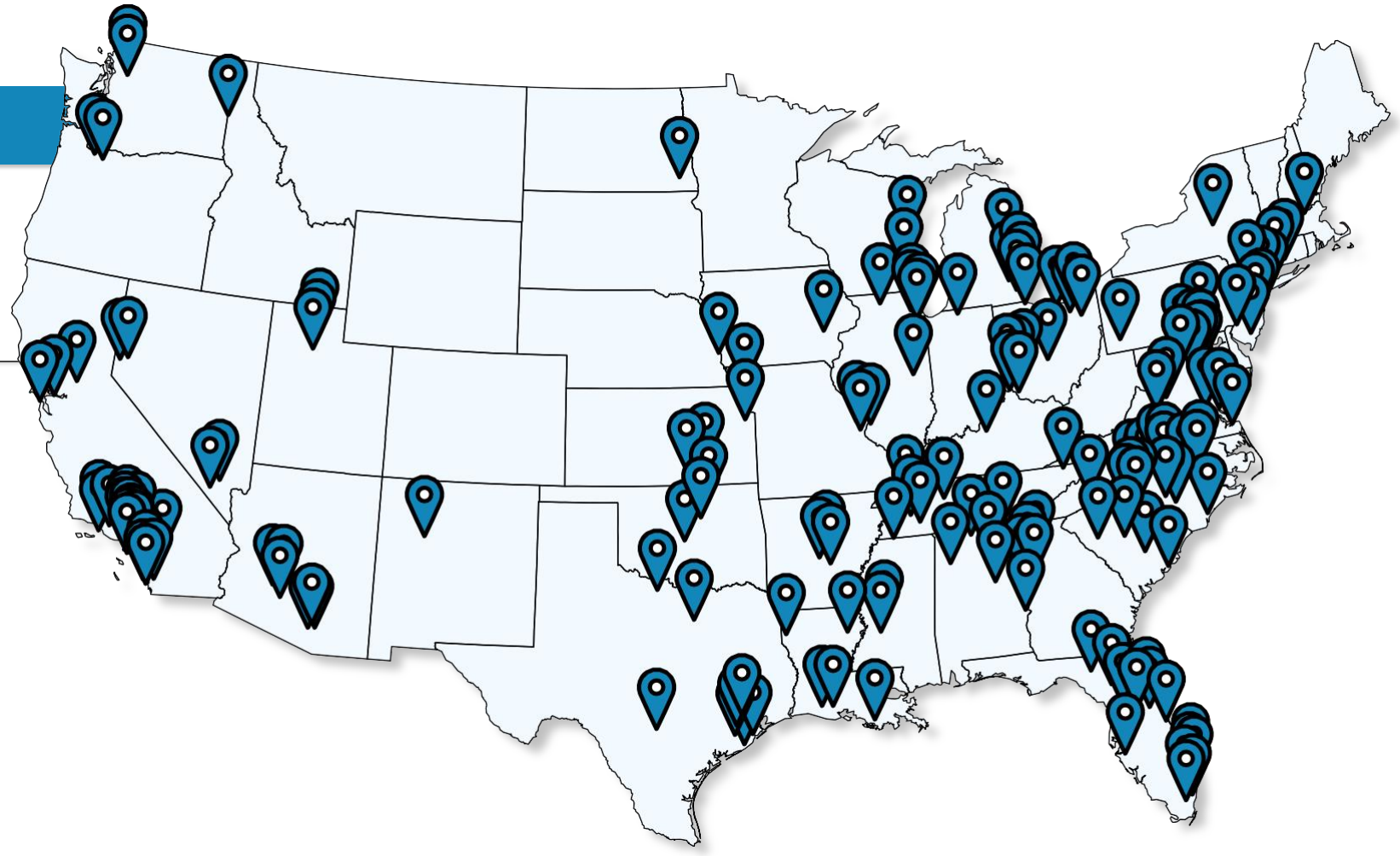
Inclusion Criteria	Exclusion Criteria
▪ 45 – 84 years old ▪ Average risk for CRC ▪ Intended to undergo colonoscopy ▪ Consent to blood draw and colonoscopy within 60 days* ▪ Consent to follow-up for 2 years as per protocol	▪ History of cancer, inflammatory bowel disease ▪ Hereditary predisposition to CRC or history of CRC in first degree relative ▪ Colonoscopy within preceding 9 years ▪ Positive fecal immunohistochemical (FIT) or fecal occult blood test (HSgFOBT) within previous 6 months ▪ Completed mt-sDNA or mSEPT9 testing within previous 3 years

***Due to impacts of COVID-19 pandemic, window for colonoscopy completion extended from 60 to 183 days for those enrolled after 1/20/2020**

Individuals Enrolled From 265 Sites in United States to Ensure Broad Demographic Representation

ECLIPSE Study Sites

N = 20	Academic / VA
N = 245	Community



VA = Veteran Affairs

Co-Primary Objectives Evaluated Sensitivity and Specificity of Shield Compared to Colonoscopy

Sensitivity for CRC	**Performance Goal: Lower-bound of 2-sided 95% CI > 65%**
Specificity for Advanced Neoplasia (AN)	**Performance Goal: Lower-bound of 2-sided 95% CI > 85%**

- Performance goals based on precedent for approved stool-based CRC screening tests

CI = Confidence Interval; Advanced Neoplasia defined as CRC or Advanced Adenoma

Secondary and Key Exploratory Objectives

Secondary Objective

- Sensitivity for advanced adenoma (AA)

Key Exploratory Objectives

- Positive predictive values (PPV)
- Negative predictive values (NPV)
- Performance by demographic and baseline characteristics
- Specificity, absence of any neoplastic findings
- Malignancies identified in follow-up

Target Evaluable Sample Size for Co-Primary Objectives

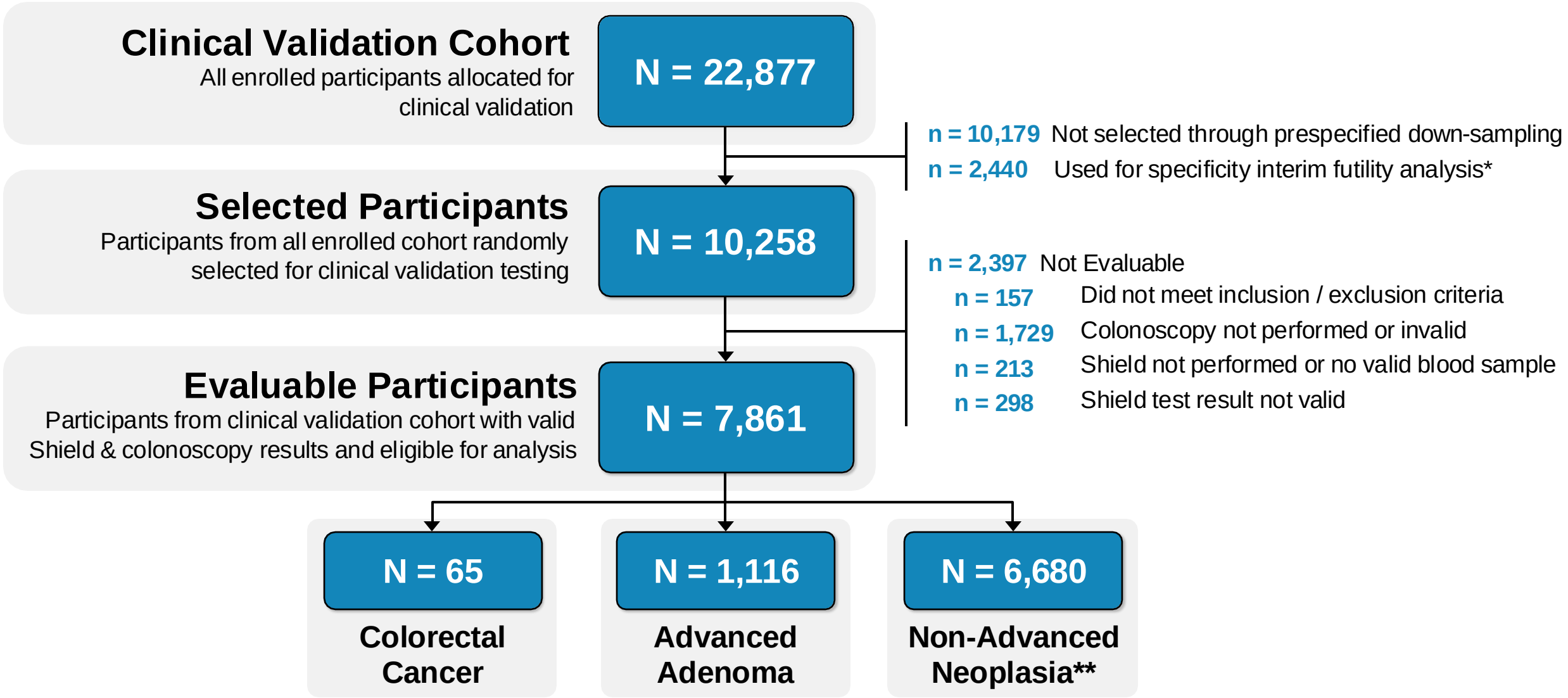
- Event-driven study design
- 68 CRCs provide 85% power for two-sided 95% CI > 65% for sensitivity
  - Assuming true Shield sensitivity = 80.7%
- 7,000 individuals negative for advanced neoplasia provide > 85% power for two-sided 95% CI > 85% for specificity
  - Assuming true Shield specificity = 86.3%

Target Evaluable Sample Size

Evaluable Individuals with CRC	68
Evaluable Individuals Negative for Advanced Neoplasia	7,000

CI = Confidence Interval

Disposition



*4 subjects in interim futility analysis were determined to not meet I/E
**Non-advanced adenomas, non-neoplastic findings, and negative colonoscopy

Baseline Demographics and Patient Characteristics

		Evaluable Cohort N = 7,861
Age, years; Mean (SD)		60 (9)
Age Group	45 – 49	8%
	50 – 69	70%
	70+	22%
Sex	Female	54%
Ethnicity	Hispanic	13%
Race	White	79%
	Black or African American	12%
	Asian	7%
	Other	2%

SD = Standard Deviation

Shield Met Co-Primary Objective of CRC Sensitivity

	Colonoscopy	Shield	
	Positive Result N	**Positive Result** N	**CRC Sensitivity** % (95% CI)
Colorectal Cancer	**65**	**54**	**83.1%** (72.2, 90.3)

Lower confidence bound > 65% performance goal

Shield Met Co-Primary Objective of Advanced Neoplasia Specificity

	Colonoscopy	Shield	
	Negative Result N	**Negative Result** N	**AN Specificity** % (95% CI)
Non-Advanced Neoplasia*	**6,680**	**5,982**	**89.6%** (88.8, 90.3)

Lower confidence bound > 85% performance goal

***Non-advanced adenomas, non-neoplastic findings, and negative colonoscopy**

Secondary Endpoint: Shield Showed 13% Sensitivity for Advanced Adenoma

	Colonoscopy	Shield	
	Positive Result N	Positive Result N	AA Sensitivity % (95% CI)
Advanced Adenoma	**1,116**	**147**	**13.2%** (11.3, 15.3)
High-Grade Dysplasia	**31**	**7**	**22.6%** (11.4, 39.8)
Villous Component	**207**	**37**	**17.9%** (13.3, 23.7)
≥ 20 mm in size	**204**	**35**	**17.2%** (12.6, 22.9)

Shield Performance Consistent Across Baseline Demographics

		CRC Sensitivity N = 65	AN Specificity N = 6,680
Age Group, years	45 – 49	75% (3 / 4)	96% (554 / 580)
	50 – 59	77% (10 / 13)	93% (2,470 / 2,657)
	60 – 69	88% (30 / 34)	90% (1,785 / 1,989)
	70 – 79	77% (10 / 13)	81% (1,136 / 1,405)
	80+	100% (1 / 1)	76% (37 / 49)
Sex	Female	87% (26 / 30)	90% (3,314 / 3,677)
	Male	80% (28 / 35)	89% (2,668 / 3,003)
Race	White	82% (40 / 49)	90% (4,672 / 5,201)
	Black or African American	90% (9 / 10)	92% (737 / 800)
	Asian	75% (3 / 4)	84% (422 / 500)
Ethnicity	Hispanic or Latino	91% (10 / 11)	87% (791 / 906)
	Not Hispanic or Latino	82% (44 / 54)	90% (5,162 / 5,741)

Shield Sensitivity Correlated with Lesion Size and Stage

		CRC Sensitivity N = 65	
Tumor Location	Proximal Colon	89%	(8 / 9)
	Distal Colon	84%	(27 / 32)
	Rectum	79%	(19 / 24)
Most Significant Lesion Size	≤ 9 mm	0%	(0 / 6)
	10 – 19 mm	88%	(7/ 8)
	≥ 20 mm	92%	(46 / 50)
	Missing	100%	(1 / 1)
CRC Tumor Stage**	Stage I*	55%	(12 / 22)
	Stage II	100%	(14 / 14)
	Stage III	100%	(18 / 18)
	Stage IV	100%	(9 / 9)

*Assumes 5 incompletely staged by AJCC malignant polyps are Stage I disease (1/5 detected)
**Excludes 2 lost to clinical follow-up (1/2 detected; 50%)

Shield Positive and Negative Predictive Values for CRC

	Observed Prevalence in ECLIPSE	PPV (95% CI)	NPV (95% CI)
Colorectal Cancer	**0.41%**	**3.03%** (2.7, 3.4)	**99.9%** (99.9, 100.0)

- Given prevalence of CRC in average-risk population, PPV and NPV in range with expectations for CRC screening test

Shield Demonstrated 89.9% Specificity in Individuals Without Any Neoplastic Findings Identified on Colonoscopy

	Colonoscopy	Shield	
	Negative Result N	Negative Result N	Specificity % (95% CI)
No Neoplastic Findings	**4,514**	**4,057**	**89.9%** (89.0, 90.7)

ECLIPSE Safety

Shield Safety Categorized into Direct and Indirect Risks

Direct Risk

Health Risks from Performing Shield

Indirect Risk

False Positives

False Negatives

Shield Presents Low Direct Risk

- No unanticipated adverse device effects across 22,877 enrolled participants
- 43 AEs reported in ECLIPSE
  - 70% (30/43) related to study phlebotomy including syncope, nausea, and hematoma
  - 30% (13/43) unrelated, includes 2 unrelated SAEs

Potential for Inaccurate Result in CRC Screening

False-Positive Shield Result

- Could lead to colonoscopy
  - Minimal added risk, as colonoscopy is recommended standard of care

Shield 1-Year Data Indicate Rate of Non-CRC Malignancies Not Increased in False Positive Results

Advanced Neoplasia	Number of Results N	1-year Follow-Up Data	
		Follow-up Available N	Rate of non-CRC malignancies % (95% CI)
Shield False Positives	**698**	**640 (92%)**	**0.8%** (5/640) (0.3, 1.8)
Shield True Negatives	**5,982**	**5,502 (92%)**	**0.9%** (51/5,502) (0.7, 1.2)

- 2-year follow-up ongoing to evaluate outcomes in individuals with false-positive Shield result

Data collection and analyses are ongoing and this update from March 2024 has not been fully reviewed by the FDA

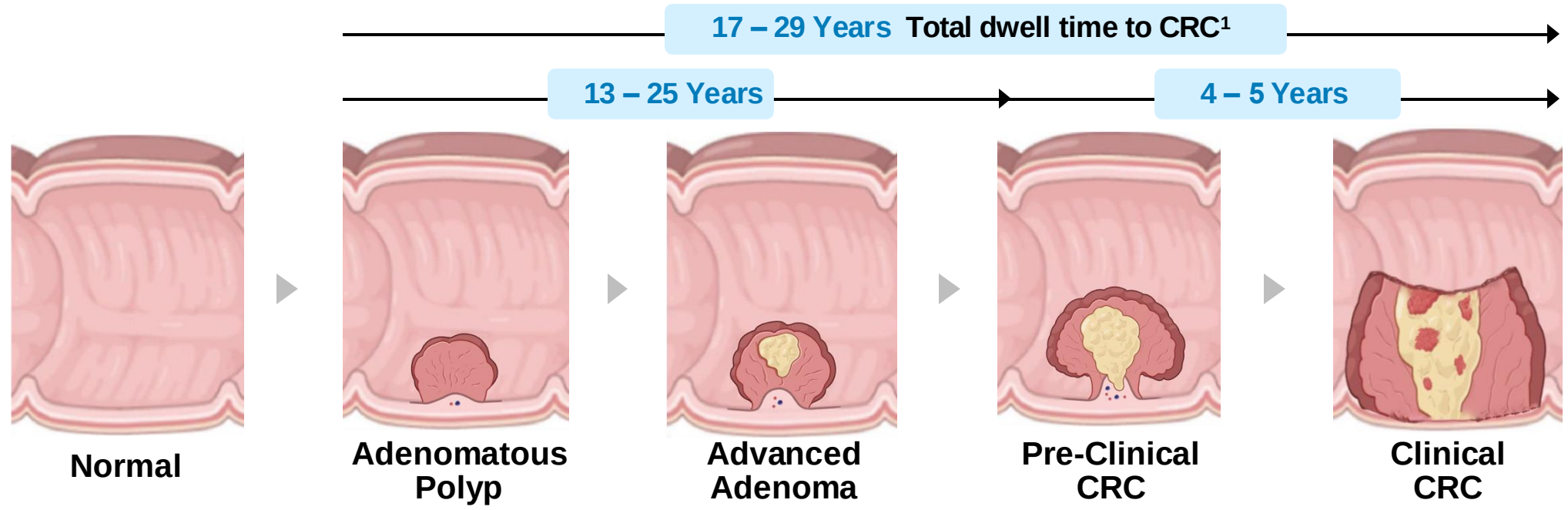
Potential for Inaccurate Result in CRC Screening

False-Negative Shield Result

- Could lead to forgoing other recommended screening
- 17% false-negative rate in range with other non-invasive CRC screening tests (e.g. 8 – 33%[1-4])
- 100% sensitivity for detecting Stage II, III, and IV CRC in ECLIPSE
  - Sensitivity for Stage I cancer (55%) in range with other noninvasive CRC screening tests (FIT 50 – 66%[2,4])

1. Lin, 2021; 2. Imperiale, 2014; 3. PMA P130017 FDA Summary of Safety and Effectiveness Data; 4. Imperiale, 2024

Biology Allows for Longitudinal Testing to Intervene to Reduce CRC Mortality



Non-invasive Tests Allow Multiple Testing Interventions

Screening Test Completion

1. Knudsen, 2021

Shield is a Safe and Effective Blood-Based Screening Test for Patients Eligible for Average-Risk CRC Screening

- Shield met prespecified acceptance criteria for both co-primary endpoints of CRC sensitivity and AN specificity
- CRC sensitivity and AN specificity consistent across baseline demographics including sex, race, and ethnicity
  - CRC sensitivity increases with stage and lesion size
  - AN specificity decreases with age
- Shield has limited detection capabilities for AA
- No unanticipated adverse device effects

ECLIPSE demonstrates strong performance and an acceptable safety profile for Shield as a primary screening option for average risk individuals

Clinical Perspective

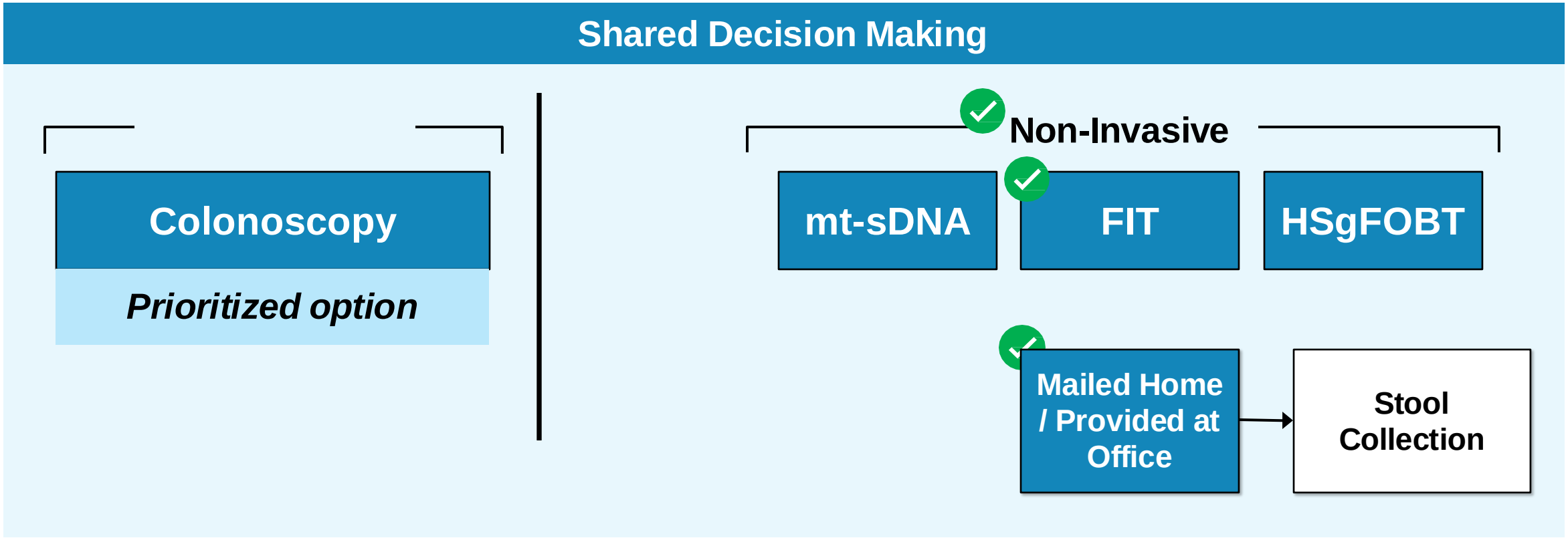
Monnie Singleton, MD

CEO and Medical Director
Singleton Health Center and Medical Center of Santee
Orangeburg County, South Carolina

Colorectal Cancer Screening Improves Survival but Millions of Eligible Individuals Not Screened

- Patients and providers need additional CRC screening options that are convenient, noninvasive, and accurate
- Potential benefits of an effective blood-based screening option
  - Enhance patient access
  - Improve adherence to screening recommendations
  - Increase number of individuals up to date with screening
  - Reduce preventable CRC deaths

Shield Would Add Effective Blood-Based Screening Option Alongside Guideline-Recommended Stool-Based Tests



Patients do not decline stool tests, they do not complete them

Tracking and monitoring completion often challenging in primary care setting

Shared Decision-Making Plays a Crucial Role in Test Selection to Maximize Adherence

MAXIMIZE SCREENING FOLLOW-THROUGH

Screening interventions higher among patients **offered options** in line with preferences[1]

Offering test choice has been shown to increase adherence[1-3]

MINIMIZE LIKELIHOOD OF NONADHERENCE

Patient may not adhere with screening if the test offered is seen as undesirable[1]

ACHIEVE GUIDELINE SCREENING TARGETS

80% screening target for adults 45 years and older

Discussion of all options with patients will maximize screening uptake and possibility test is completed[4]

1. Volk, 2018; 2. Inadomi, 2012; 3. Wolf, 2018; 4. Davidson, 2021

NCCRT Manual Provides Key Facts for PCPs when Discussing CRC Screening Options with Patients

Colonoscopy

- **Reduces death from CRC**
- **Can prevent cancer** by removing polyps (or abnormal growth) during test
- Examines entire colon
- Finds most cancers or polyps present at time of test
- Done every 10 years if no polyps are found

HSgFOBT / FIT

- **Reduces death from CRC**
- Safe, available, and easy to complete
- Done on your own at home and returned
- Finds most cancers early by finding blood in stool
- Done annually if negative

mt-sDNA

- **Reduces death from CRC**
- Safe, available, and easy to complete
- Done on your own at home and returned
- Finds most cancers early by finding blood or altered DNA in stool
- Done every 3 years if negative

National Colorectal Cancer Roundtable Manual for Primary Care Practices, 2022

Shield Effectively Detects CRC, With Performance in Range of Primary Stool-Based Screening Tests

	Current Primary Non-Invasive Stool CRC Tests			Blood Test
	mt-sDNA	FIT	HSgFOBT	Shield
CRC Sensitivity[1-5]	92%	67 – 74%	68%	83%
AN Specificity[1-5]	87%	95%	97%	90%
AA Sensitivity[1-5]	42%	23 – 24%	11%	13%

1. PMA P130017 FDA Summary of Safety and Effectiveness Data; 2. Imperiale, 2014; 3. Imperiale 2024; 4. Lin, 2021; 5. Chung, 2024

Shield is a Safe and Effective Test for Use as a Primary Screening Option Similarly to Other Non-Invasive Tests

Shared Decision Making

Visualization

- **Colonoscopy**
  - *Prioritized option*

Non-Invasive

- **mt-sDNA**
- **Shield**
- **FIT**
- **HSgFOBT**

Promote shared decision-making rather than restrict access to effective screening tests

The 'best' screening test is the one that gets done.

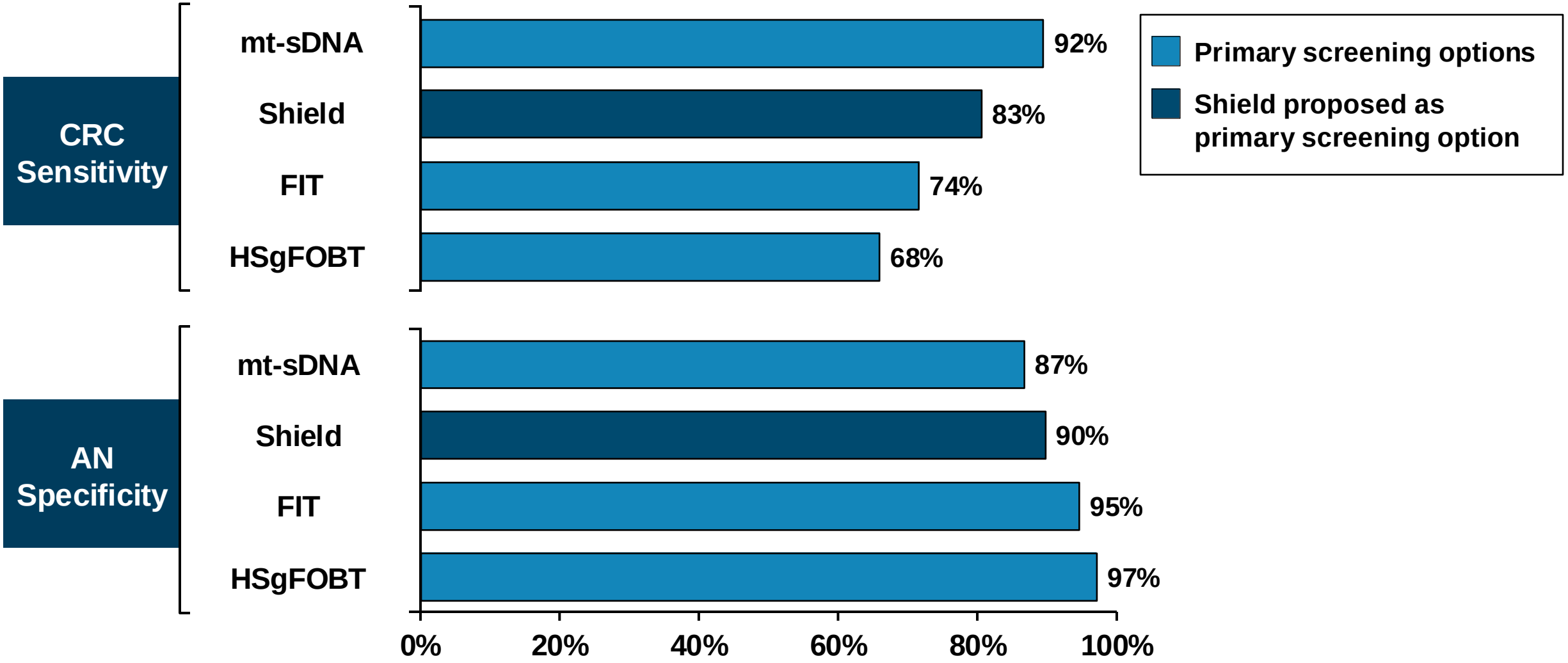
Conclusion

Craig Eagle, MD

Chief Medical Officer

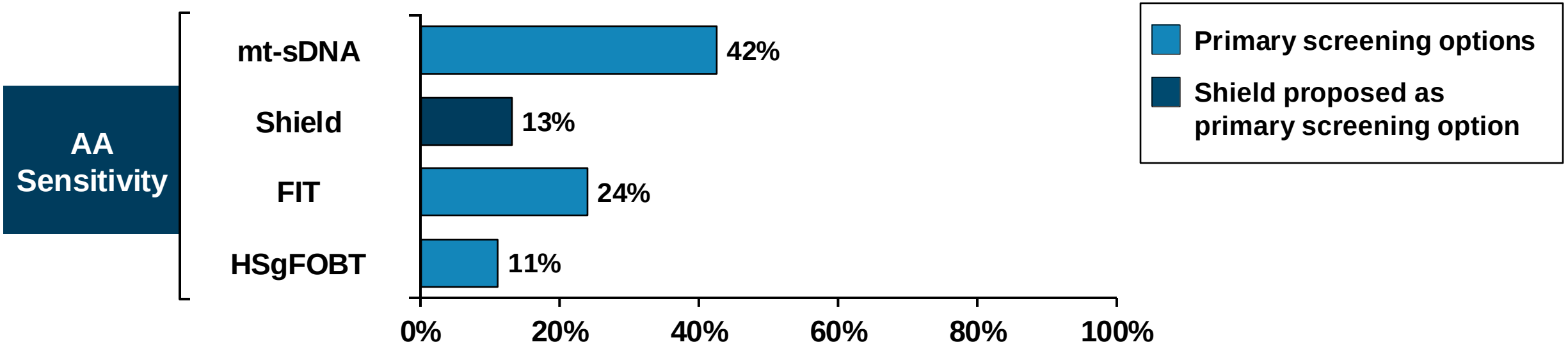
Guardant Health

Shield IU is to Detect CRC, and Data is in Range with Non-Invasive CRC Screening Modalities



PMA P130017 FDA Summary of Safety and Effectiveness Data; Chung, 2024; Imperiale, 2014; Lin, 2021

Shield's AA Performance is in Lower-End Range of Performance of Stool Tests

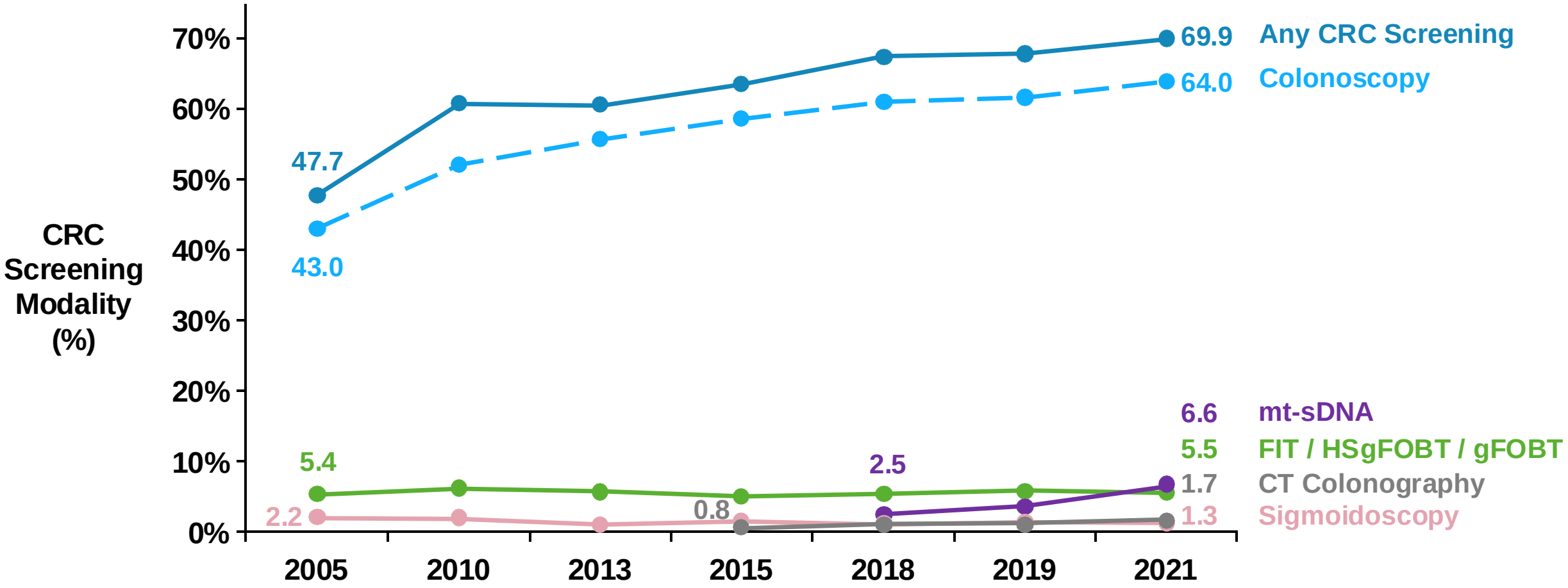


- Colonoscopy is the most accurate test for AA detection (up to 95%*)
- Shield's proposed indication is to detect CRC

*** ≥ 10 mm adenomas**

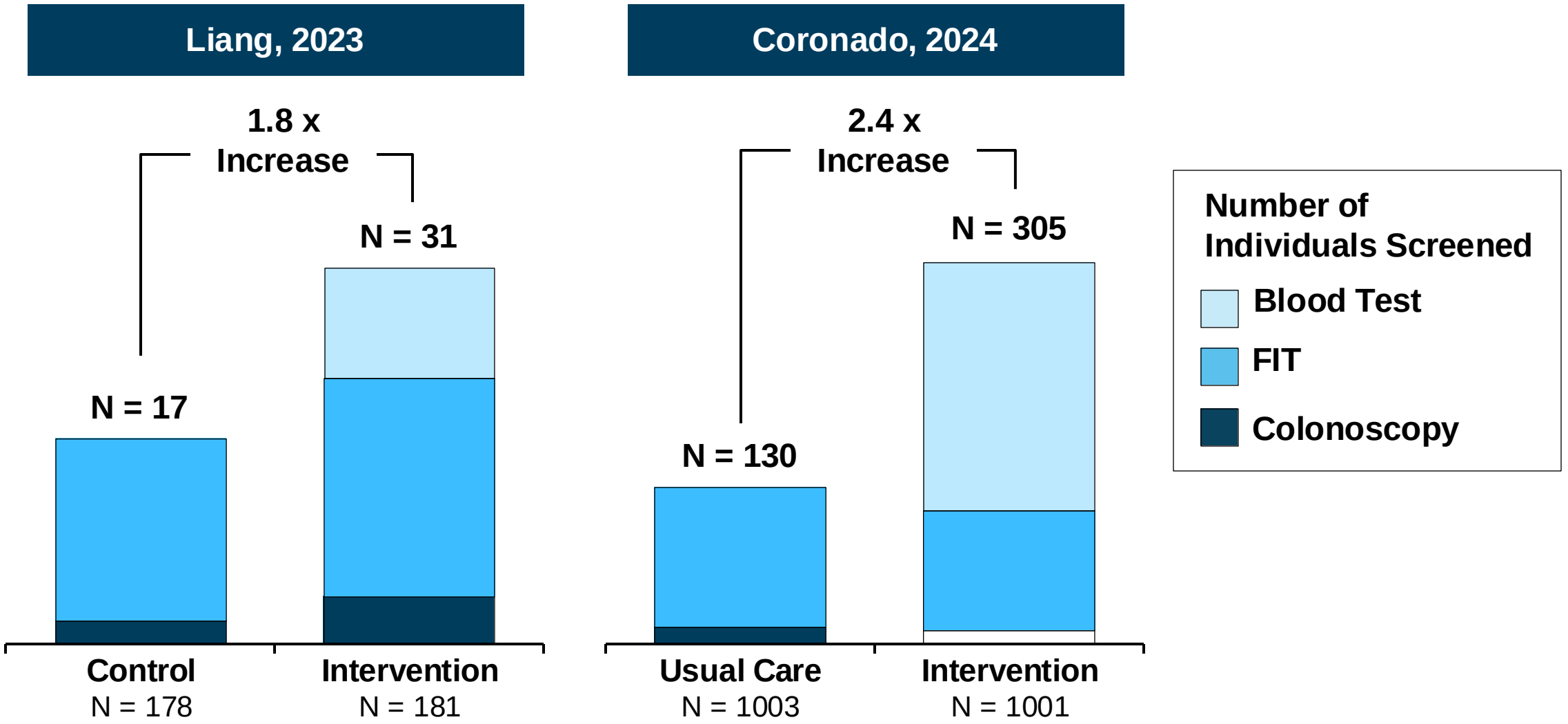
PMA P130017 FDA Summary of Safety and Effectiveness Data; Chung, 2024; Imperiale, 2014; Lin, 2021

Offering More Screening Options Increases Screening Rates Overall with Minimal Impact on Current Tests



Adapted from Ebner, 2024

CRC Screening Rates Increase When Blood Test is Offered Without Significant Test Substitution



Liang, 2023; Coronado, 2024

Primary Test Choice

*“There is evidence that patients **will have a preference** for one type of screening test over others **if provided sufficient information** regarding these test attributes, although no single test appears to consistently dominate patient preferences, **supporting a strategy of offering choice.***

Intention to screen is also higher if the screening test ordered is consonant with the patient's preference.”

American Cancer Society

Wolf, 2018

Guardant Health Committed to Patient and Provider Education to Facilitate Informed Shared-Decisions

- Education outlining Shield's performance (incl. AA performance), benefits and limitations including
  - Implications of a "false positive" or "false negative"
  - Repeat testing for "Normal Signal Detected"
  - Colonoscopy for "Abnormal Signal Detected"
- Convened independent group of communication experts to ensure accuracy and comprehension of educational materials
- Align with FDA to ensure communication channels to patients and physicians are considered
  - e.g. educational videos, online training, provider scripts, etc.

Guardant Health Committed to Building Evidence Including Long-term Data

- ECLIPSE long-term 1- and 2-year cancer follow-up visits
  - 92% of participants (N=7,169) completed 1-year follow-up

- Committed to further studies in collaboration with FDA, guideline committees, CRC screening experts, and community to address
  - Individuals with false-positives
  - Longitudinal adherence
  - Diagnostic colonoscopy rates
  - Cumulative PPV (to inform test interval)

Shield is a Safe and Effective Primary Screening Option with Population Benefit

Shield as Primary Screening Option

- Shield's performance in range of non-invasive stool tests
- Can increase impact of opportunistic health visit
- Patients do not decline stool tests, they do not complete them
- Sequential testing will have negative impact on population benefit
  - Create access barriers to screening completion
  - Generate misperception of the test
- Goal should be to promote informed shared-decision making with labeling, education materials, and fact sheets.

Shield is a Blood Based Colorectal Cancer Screening Test for Average-Risk Adults

May 23, 2024

Molecular and Clinical Genetics Panel

Guardant Health

Which Screening Test Is Right for You?

Differences in Colon Cancer Screening

Test Result	Test Type: Colonoscopy	FIT*	HSgFOBT*	FIT-DNA*
Can detect colon cancer	✓	✓	✓	✓
Can prevent colon cancer	✓	*	*	*
Requires a follow-up test (colonoscopy) if results are abnormal	–	✓	✓	✓
Test Process				
You do this test at home	–	✓	✓	✓
Requires you to handle stool (feces)	–	✓	✓	✓
You do the test once a year	–	✓	✓	–
You do the test once every three years	–	–	–	✓
You do the test once every 10 years	✓	–	–	–
A health care provider does this test in a medical office or hospital	✓	–	–	–
Requires a special diet the day before	✓	–	–	–
May require diet restriction a few days before	–	–	✓	–
Usually includes anesthesia before	✓	–	–	–
Is a procedure to look inside the colon	✓	–	–	–
Includes a risk of rare complications, such as colon perforation or bleeding	✓	*	*	*
Requires an escort home	✓	–	–	–

*If this test shows abnormal results, further testing is needed by colonoscopy. If the follow-up colonoscopy detects abnormal growths or polyps, removing them can help prevent cancer.