Clinical Validation of a Cell-free DNA Blood-based Test for Colorectal Cancer Screening in an Average Risk Population

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Background

- Despite the widespread availability of many CRC screening options, there are persistent barriers and **screening rates remain suboptimal**[1]

  - Approximately 59% of eligible individuals aged 45 years+ are adherent[2], well below the target of 80%[3]

- A blood-based CRC screening test, completed as part of a routine health care encounter, presents an opportunity to increase adherence to CRC screening[4]

- We report the performance of a cell-free DNA (cfDNA) blood-based CRC screening test in an average-risk population undergoing screening colonoscopy.

cfDNA blood-based CRC screening test

Genomic Alterations

Epigenomic Modifications

Results

Mutations known to be present in CRC

DNA methylation

DNA fragmentation pattern

Integrate these signals to produce an **actionable result**

🔴 **Abnormal** Signal Detected

🟢 **Normal** Signal Detected

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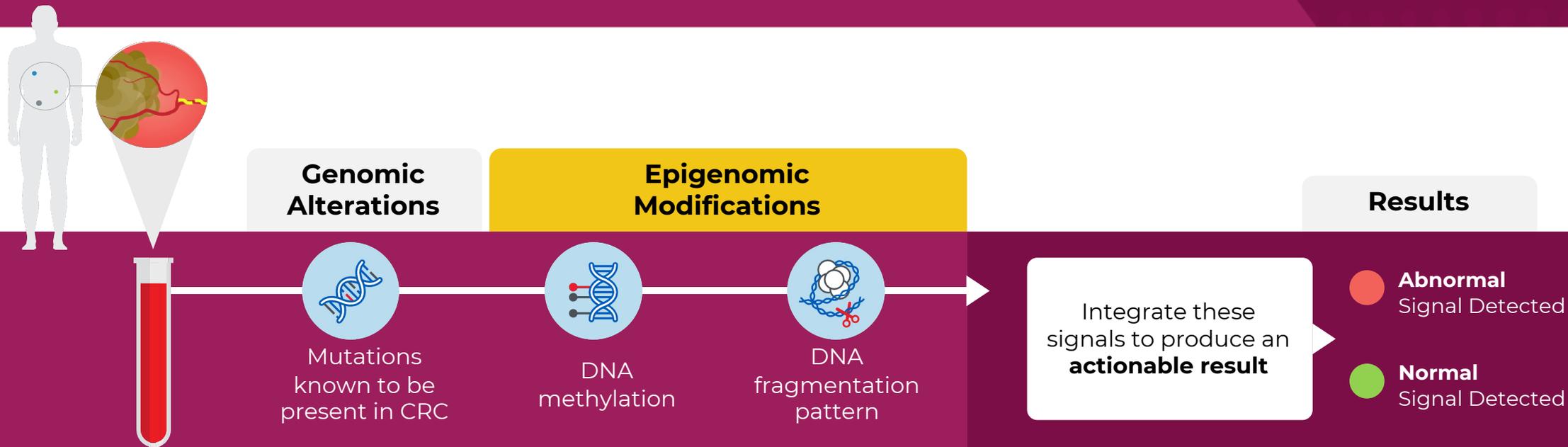
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5) D'Auria, et al. 2022. Journal of Clinical Oncology supplement

ECLIPSE - Evaluation of the ctDNA LUNAR-2 Test in an Average Patient Screening Episode

Inclusion criteria:

☑ Average risk for CRC

☑ Age 45-84

☑ No CRC familial predisposition

☑ No recent CRC screening

☑ No prior history of cancer or inflammatory bowel disease

Whole blood collected prior to screening colonoscopy and associated preparation

Screening Colonoscopy

+

Blood-based CRC screening Test

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Study objective: test performance as compared to colonoscopy with histopathology

Co-Primary Endpoints	CRC sensitivity	Advanced Neoplasia (AN)* Specificity
Acceptance Criteria	Lower-bound of 2-sided 95% Wilson CI > 65%	Lower-bound of 2-sided 95% Wilson CI > 85%
Enrollment	65 evaluable individuals with CRC	Target sample size of 7,000 with non-CRC: 80% power to establish specificity > 85% Stratified random sampling such that age distribution of the non-CRC subjects followed the 2020 US age distribution

*Advanced neoplasia (AN): CRC or advanced precancerous lesion

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Enrolled Participants
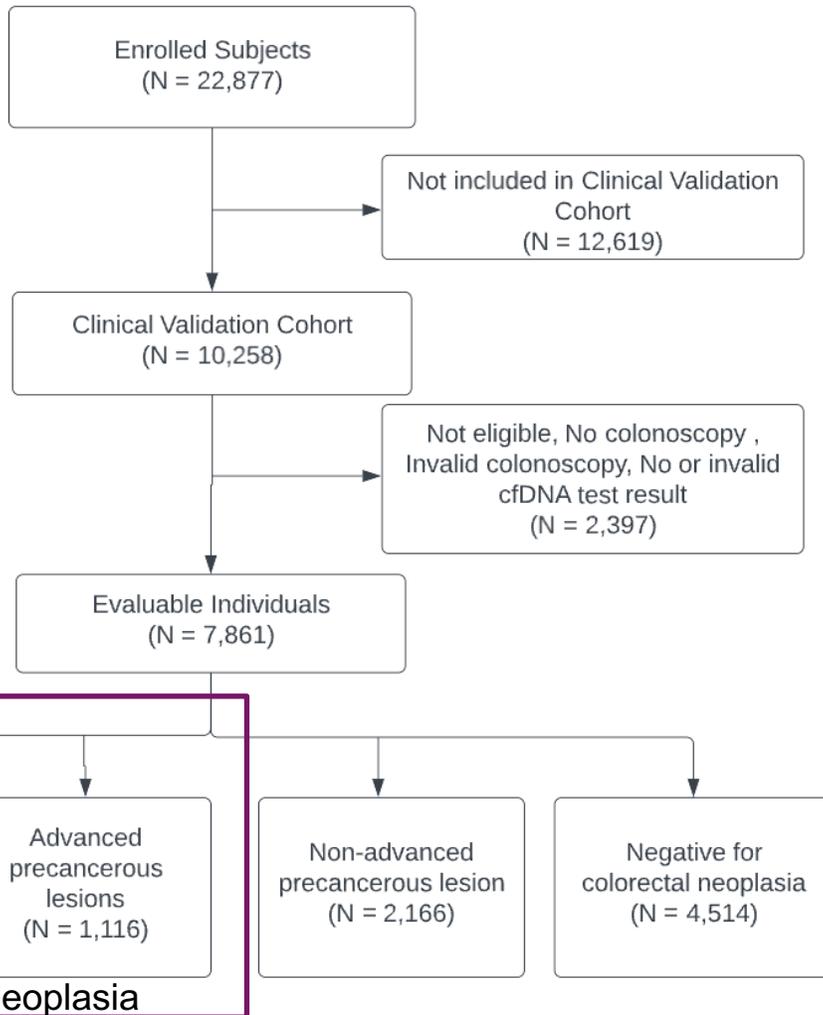
Colonoscopy Outcome	Histopathology Definition
CRC	CRC
Advanced Precancerous Lesion	Carcinoma in situ High Grade Dysplasia Villous architecture >25% Tubular Adenoma > 10mm Sessile Serrated Lesion > 10mm
Non-advanced precancerous lesion	Adenoma and sessile serrated lesion < 10mm
Negative for colorectal neoplasia	Negative colonoscopy Hyperplastic polyps

Flowchart:

Enrolled Subjects (N = 22,877)
→ Not included in Clinical Validation Cohort (N = 12,619)

Clinical Validation Cohort (N = 10,258)
→ Not eligible, No colonoscopy, Invalid colonoscopy, No or invalid cfDNA test result (N = 2,397)

Evaluable Individuals (N = 7,861)

- CRC (N = 65)
- Advanced precancerous lesions (N = 1,116)

Advanced Neoplasia

- Non-advanced precancerous lesion (N = 2,166)
- Negative for colorectal neoplasia (N = 4,514)

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ECLIPSE enrollment reflective of diverse US population

Characteristic	Clinical Validation Cohort (N=10,258)	Evaluable Subjects (N=7,861)
Age (years)		
Mean (SD)	60.6 (9.13)	60.3 (9.14)
Min, Max	45, 90	45, 84
Age Group (years)	N (%)	N (%)
45-49	776 (7.6)	640 (8.1)
50-69	7,161 (69.8)	5,495 (69.9)
70+	2,321 (22.6)	1,726 (22.0)
Sex		
Female	5,493 (53.5)	4,218 (53.7)
Race		
American Indian or Alaska Native	19 (0.2)	14 (0.2)
Asian	685 (6.7)	560 (7.1)
Black or African American	1,353 (13.2)	931 (11.8)
Native Hawaiian or Other Pacific Islander	24 (0.2)	19 (0.2)
White	7,939 (77.4)	6,167 (78.5)
Other / Multiple / Missing	238 (2.3)	170 (2.2)
Ethnicity		
Hispanic or Latino	1,561 (15.2)	1,044 (13.3)

ECLIPSE: Enrolled **>20% of participants identifying as non-white,** mirroring the US population[6]

>200 rural and urban sites, including community hospitals, private practices, GI clinics and academic centers

34 states across every geographic region

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ECLIPSE met co-primary endpoints

CRC Sensitivity

Specificity

83%

90%

N = 65

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Stage Specific CRC Sensitivity

Stage I – III Sensitivity: 81%#
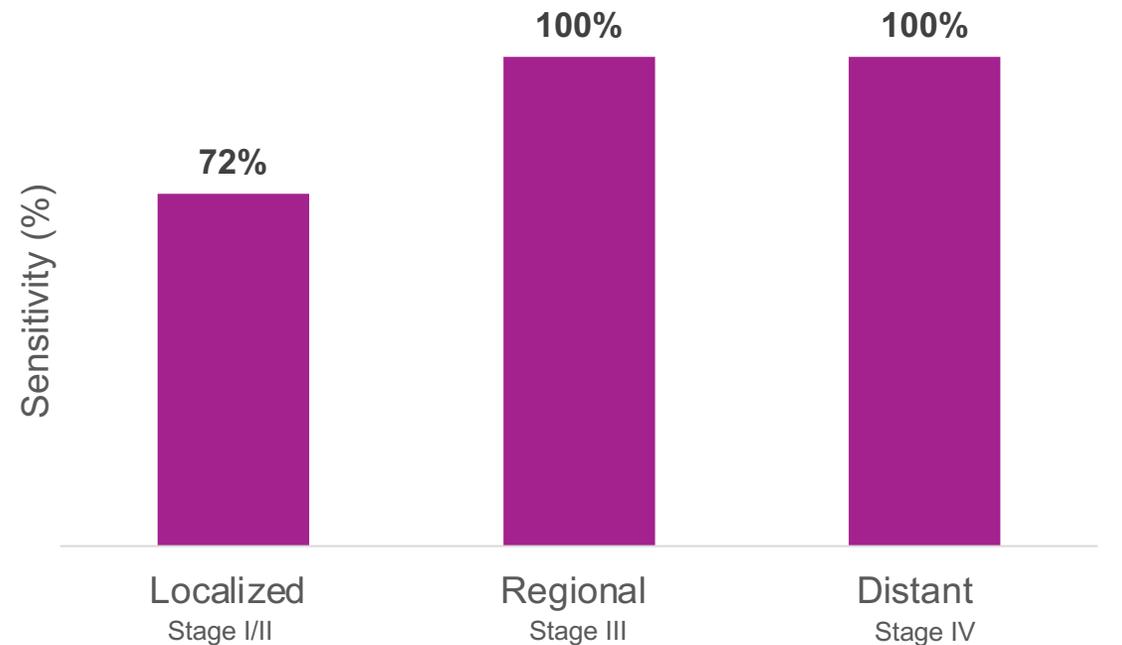
Excludes 3 lost to clinical follow-up (2/3 detected)

Stage I*	Stage II	Stage III	Stage IV
55%	100%	100%	100%
(12/22)	(14/14)	(16/16)	(10/10)

*Assumes 5 incompletely staged malignant polyps are Stage I disease (1/5 detected)

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Advanced Precancerous Lesion Detection

Most advanced finding on Colonoscopy	Positive Results	Sensitivity
Advanced Lesions	1116	147	13%
High Grade Dysplasia	31	7	23%

- No significant differences in APL sensitivity based on key clinical characteristics
- Sensitivity for more advanced pathology trended higher

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cfDNA blood-based test: potential to have high impact on CRC screening

	CRC Sensitivity[7,8] (From Literature)	Patient Adherence Rates[9-15] (From Literature)
cfDNA Blood Test	83%	85 - 96%[16]
Colonoscopy	95%	28 - 59%
FIT stool test	74%	43 - 65%
Multitarget stool DNA test	92%	48 - 71%

Screening programs require consideration of clinical effectiveness: performance of the test under **real world conditions integrating patient adherence rates**[15]

The cfDNA blood-based test has the potential to be a highly effective CRC screening option

7) Imperiale, et al. 2014. NEJM; 8) Knudsen, et al. 2021. JAMA; 9) Lin JS, et al. 2021. Agency for Healthcare Research and Quality; 10) Bretthauer, et al. 2022. NEJM; 11) Forsberg, et al. 2022. Lancet Gastroenterol Hepatol; 12) Quintero, et al. 2012. NEJM.; 13) Jensen, et al. 2016. Ann Intern Med; 14) Bakker, et al. 2011. Endoscopy; 15) Singal, et al. 2014. Clin Transl Gastroenterol; 16) Guardant Health internal data

Future Directions

- Real world clinical use and uptake – ongoing

- Understanding the impact of this blood-based test and high adherence on life years gained and number of downstream colonoscopies to help inform clinical use

- Further assay development to expand detection capabilities

- 1- and 2-year health outcomes

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Conclusions

- This cfDNA blood-based test demonstrates **83% sensitivity, 90% specificity** in average-risk CRC screening, including clinically relevant Stage I-III CRCs

- The ECLIPSE study diversity is reflective of the demographics of the intended use population in the US

- This cfDNA assay is the **first blood-based test with performance comparable to current guideline-recommended non-invasive CRC screening options**

- Combined with improved adherence with blood-based diagnostics, this cfDNA test is poised to have a significant impact on CRC screening in the population

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Questions

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Thank you!

- Healthy individuals who volunteered their participation in ECLIPSE.
- Site investigators and study staff for their collaboration throughout the COVID pandemic
- Co-authors and study team

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