Changing Landscape of Colorectal Cancer Screening

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Disclosures

- Scientific consultant Freenome Inc, Geneoscopy, UniversalDx, Iterative Health

Outline

01

Current Screening Gaps

Identify key areas where colorectal cancer screening falls short of optimal coverage and effectiveness

02

Emerging Testing Options

Explore innovative blood-based and enhanced stool-based screening technologies entering clinical practice

03

Clinical Implications

Summarize actionable insights for improving patient outcomes through enhanced screening strategies

Guidelines agree on age 45 for average risk screening

ACG

- Recommended in all adults 50 to 75 years of age
- Suggest in all average risk adults 45 to 49 years of age
- Recommend decision to screen after 75 be individualized

USPSTF

- Recommended in all adults 50 to 75 years of age
- Recommended in adults 45 to 49 years of age
- Recommended that clinicians selectively offer screening in adults 76-85 years of age

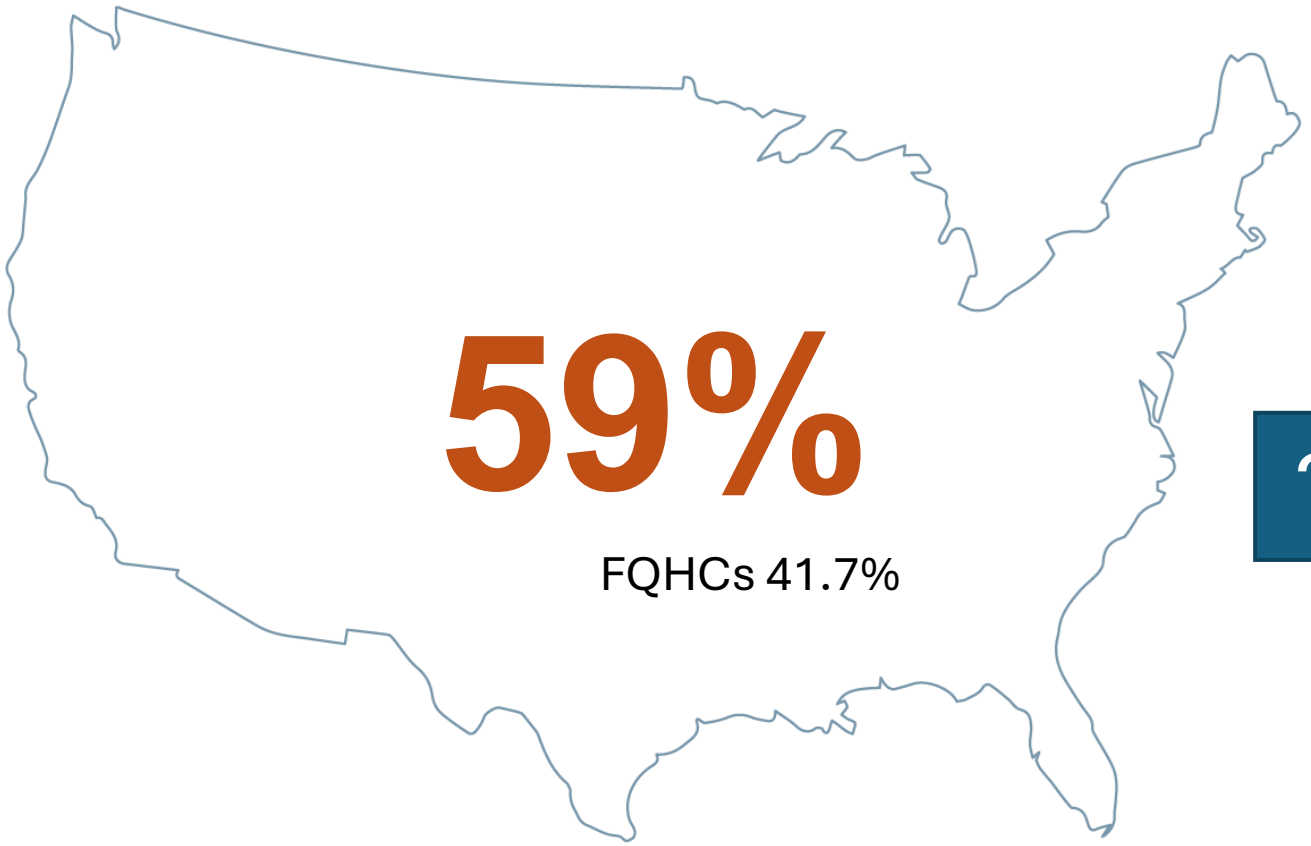
MSTF

- Suggested to all average-risk adults ages 45 to 49
- For adults ages 76 to 85, the decision to start or continue screening should be individualized and based on prior screening history, life expectancy, CRC risk, and personal preference
- Screening is not recommended after age 85

- Shaukat A. et al ACG Clinical Guidelines: AJG 2021;116:458-479; USPSTF. JAMA. 2021;325:1965-1977. Patel SG, et al. Am J Gastro. 2022. 117:57-69.

Despite Existing Screening Options, Many Eligible Patients Are Not Getting Screened for CRC

CRC screening rates, adults aged 45+



59%

FQHCs 41.7%

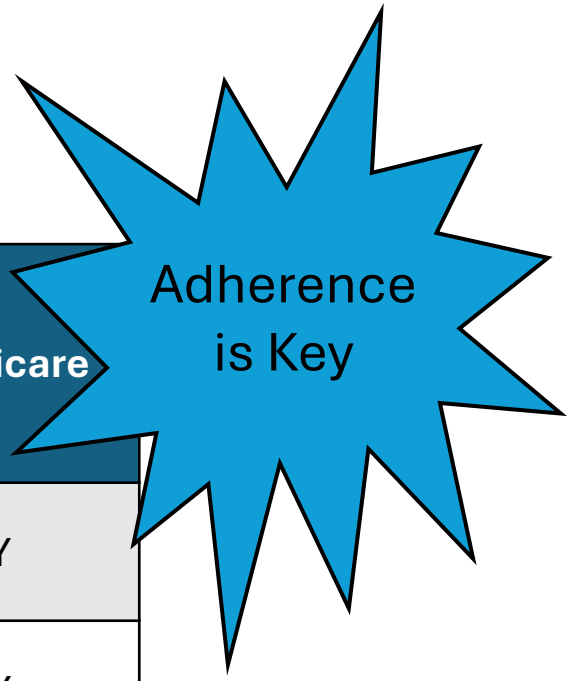
?

80%

Siegel RL et al. Colorectal cancer statistics, 2023. *CA: A Cancer J for Clinicians*. 2023. doi: 10.3322/caac.21772.c

CRC Screening Options

Modality	Sensitivity CRC	Sensitivity AA	Specificity	Invasive	USPSTF	Medicare
Colonoscopy	96%	95%	100%	Y	Y	Y
FIT	74%	24%	96%	N	Y	Y
mtsDNA stool	92%	42%	87%	N	Y	Y



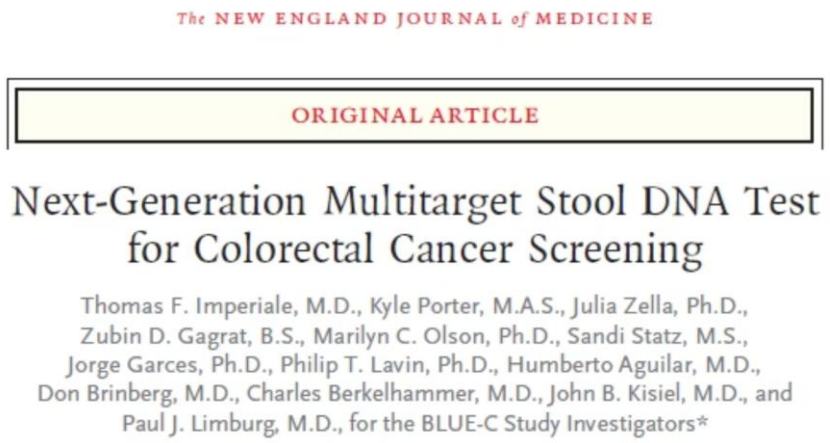
Advances

Blood-Based and Next-Generation Stool Tests Developed

Test Category	Technology	Study Details	Timeline
Stool-Based	Exact Sciences mtsDNA+FIT v2.0	Target recruitment: 29,000 participants	Completed 2023
	Geneoscopy mts-RNA	Target recruitment: 10,000 participants	Completed 2022
Blood-Based	Freenome AI-enhanced ctDNA	25,000 average-risk adults 45-85 (NCT04369053)	Completed 2022
	Guardant LUNAR ctDNA	10,000 average-risk adults 45-84 (NCT04136002)	Completed 2022

Shaukat A, Levin T R. Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol*. 2022.

Cologuard Plus: Enhanced Stool-Based Screening



Blue-C Study Design

- **20,176** participants
- Triple comparison: FIT, mtsDNA, colonoscopy
- Comprehensive biomarker analysis

Study Population

98

Colorectal Cancer Cases

2,144

Advanced Adenomas

10,961

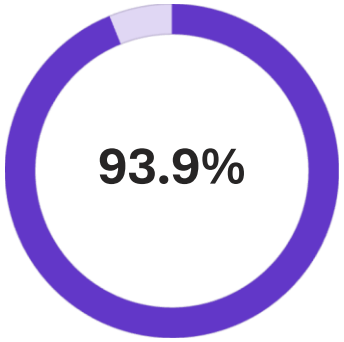
Negative Colonoscopies

Enhanced Marker Panel

- Fecal hemoglobin (FIT)
- Methylated DNA: *LASS4, LRRC4, PPP2R5C*
- Reference marker: *ZDHHC1*

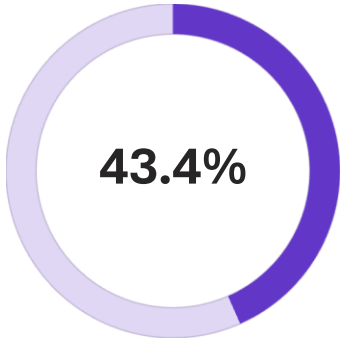
Imperiale et al. *NEJM*. 2024.

Cologuard Plus: Clinical Performance



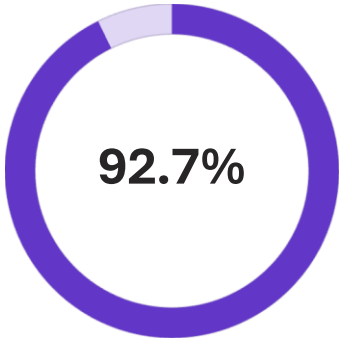
CRC Sensitivity

Excellent detection of colorectal cancer cases



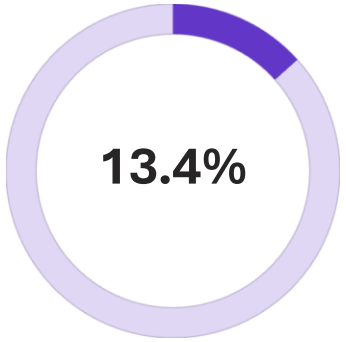
Advanced Adenoma Sensitivity

Improved precancerous lesion detection



Specificity

High accuracy in ruling out disease



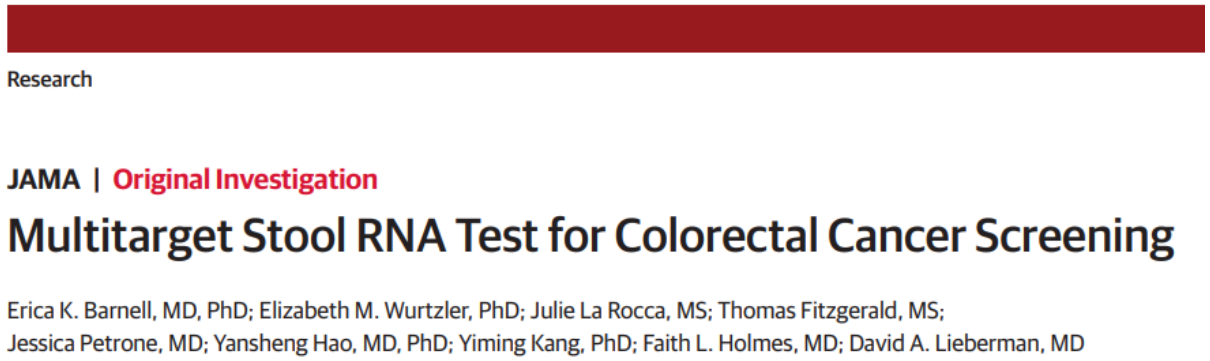
Positivity Rate

Approximately 1 in 7 tests positive

Key Insight: Cologuard Plus demonstrates significant improvements in sensitivity while maintaining high specificity, representing a meaningful advance in non-invasive screening technology.

Imperiale et al. *NEJM*. 2024.

ColoSense (mt sRNA)



Research

JAMA | Original Investigation

Multitarget Stool RNA Test for Colorectal Cancer Screening

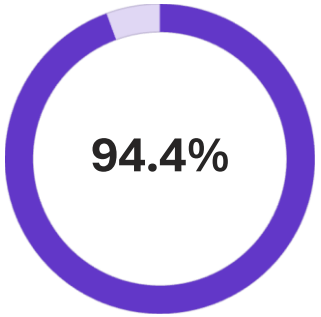
Erica K. Barnell, MD, PhD; Elizabeth M. Wurtzler, PhD; Julie La Rocca, MS; Thomas Fitzgerald, MS; Jessica Petrone, MD; Yansheng Hao, MD, PhD; Yiming Kang, PhD; Faith L. Holmes, MD; David A. Lieberman, MD

- Test uses a commercially available FIT and 8 RNA transcripts, along with participant-reported smoking status

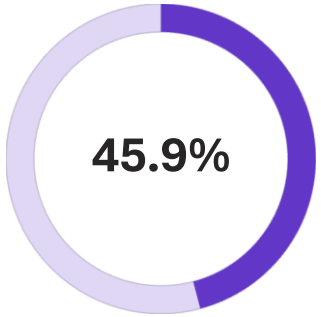
- CRC-PREVENT study
- n=8920 participants across US
- All participants had FIT, mt sRNA, and colonoscopy
- n=36 with colorectal cancer
- n=606 with advanced adenomas
- n=3760 negative colonoscopy

Barnell et al. *JAMA*. 2024.

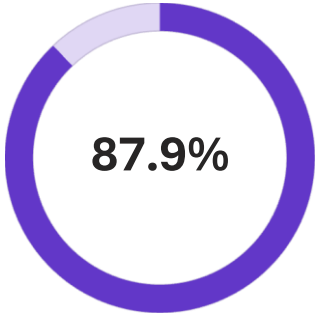
ColoSense (mt sRNA): Clinical Performance



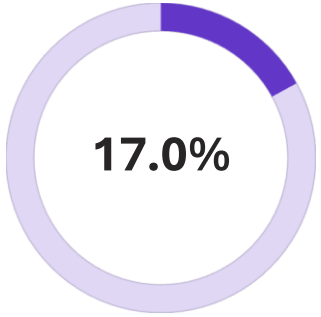
CRC Sensitivity



Advanced Adenoma Sensitivity



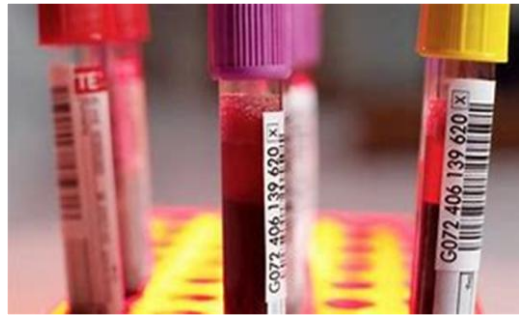
Specificity

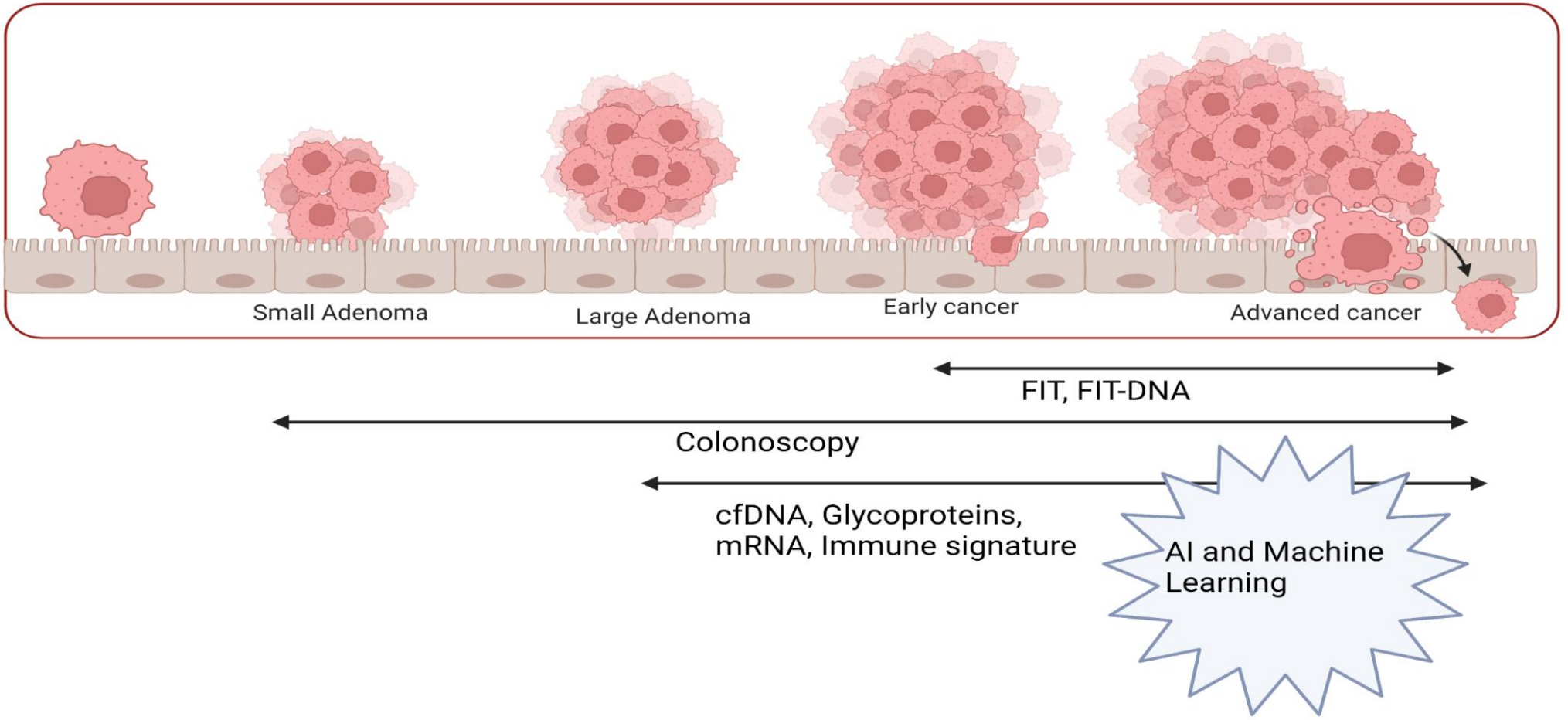


Positivity Rate

Barnell et al. *JAMA*. 2024.

Blood Based CRC Screening Tests





A Cell-Free DNA Blood-Based Test for Colorectal Cancer Screening (SHIELD)

- 22,877 individuals from 26 US sites
- Ages 45-84 and due for average risk screening
- Blood draw <= 60 days prior to screening colonoscopy
- October 2019-Sept 2022
- 7861 eligible and included

Chung et al. *NEJM*. 2024; 390:973-83.

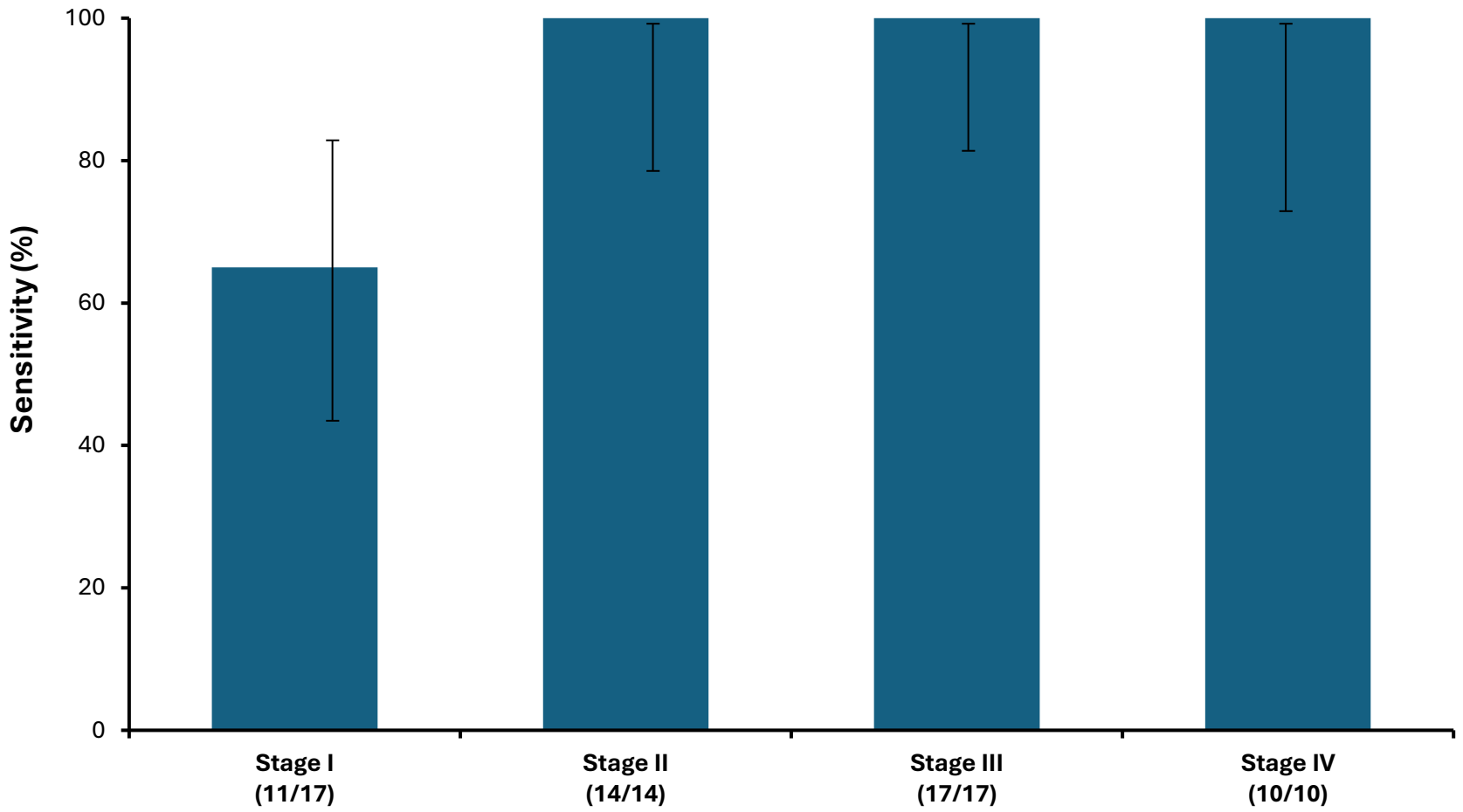
Results

Table 2. Sensitivity and Specificity of the Cell-free DNA (cfDNA) Blood-Based Test for the Most Advanced Findings on Colonoscopy.*

Variable	Most Advanced Finding on Colonoscopy	cfDNA Blood-Based Test	
		Positive Test	Sensitivity (95% CI)
	no.	*no.*	%
Colorectal cancer			
Any	65	54	**83.1 (72.2-90.3)**
Stage I, II, or III*	48	42	87.5 (75.3-94.1)
Advanced precancerous lesions†	1116	147	**13.2 (11.3-15.3)**
			Specificity (95% CI)
Nonadvanced adenomas, nonneoplastic findings, and negative colonoscopy	6680	698	**89.6 (88.8-90.3)**
Nonneoplastic findings and negative colonoscopy	4514	457	89.9 (89.0-90.7)

*Excluded were 10 stage IV and 7 pathologically confirmed, incompletely staged colorectal cancers.
†Advanced precancerous lesions include advanced adenomas and sessile serrated lesions at least 10 mm in the largest dimension.

Sensitivity by Cancer Stage



Stage 1: 65%

Stage 2: 100%

Stage 3: 100%

Stage 4: 100%

Unstaged: 29%

Pathology confirmed, incompletely staged cancers not shown (N=7)

Chung et al. *NEJM*. 2024; 390:973-83.

A Cell-Free DNA Blood-Based Test for Colorectal Cancer Screening (FREENOME)

- 48,995 individuals from 201 US sites
- Ages 45-85 and due for average risk screening
- Blood draw <= 120 days prior to screening colonoscopy
- May 2020-April 2022
- 27,010 eligible and included

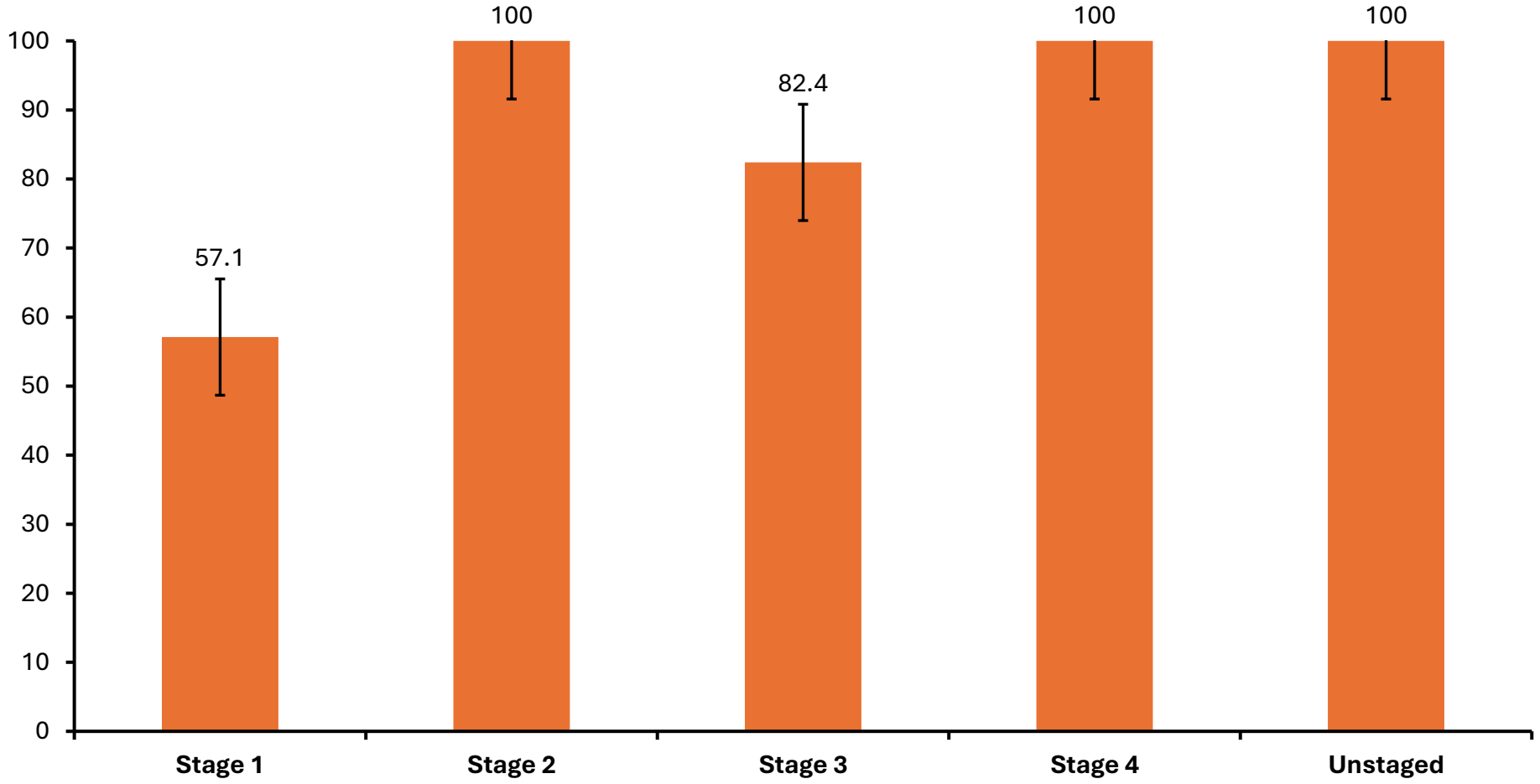
Shaukat A, Burke CA, Chan AT, Grady WM, Gupta S, Katona BW, Ladabaum U, Liang PS, Liu JJ, Putcha G, Robertson DJ, Schoen RE, Meng Z, Piscitello A, Sun CK, Xu C, Lin CJ, Lee LC, Baldo L, Levin TR; PREEMPT CRC Investigators. Clinical Validation of a Circulating Tumor DNA-Based Blood Test to Screen for Colorectal Cancer. *JAMA*. 2025 Jul 1; 334(1):56-63.

Results

	SimpleScreen (N=27,010)	
Endpoint	**Fraction (n/N)**	**Value (95% CI)**
Sensitivity for CRC	57/72	79.2% (68.4%, 86.9%)
Specificity	22,306/24,371	91.5% (91.2%, 91.9%)
Sensitivity for advanced precursor lesions	321/2567	12.5% (11.3%, 13.8%)

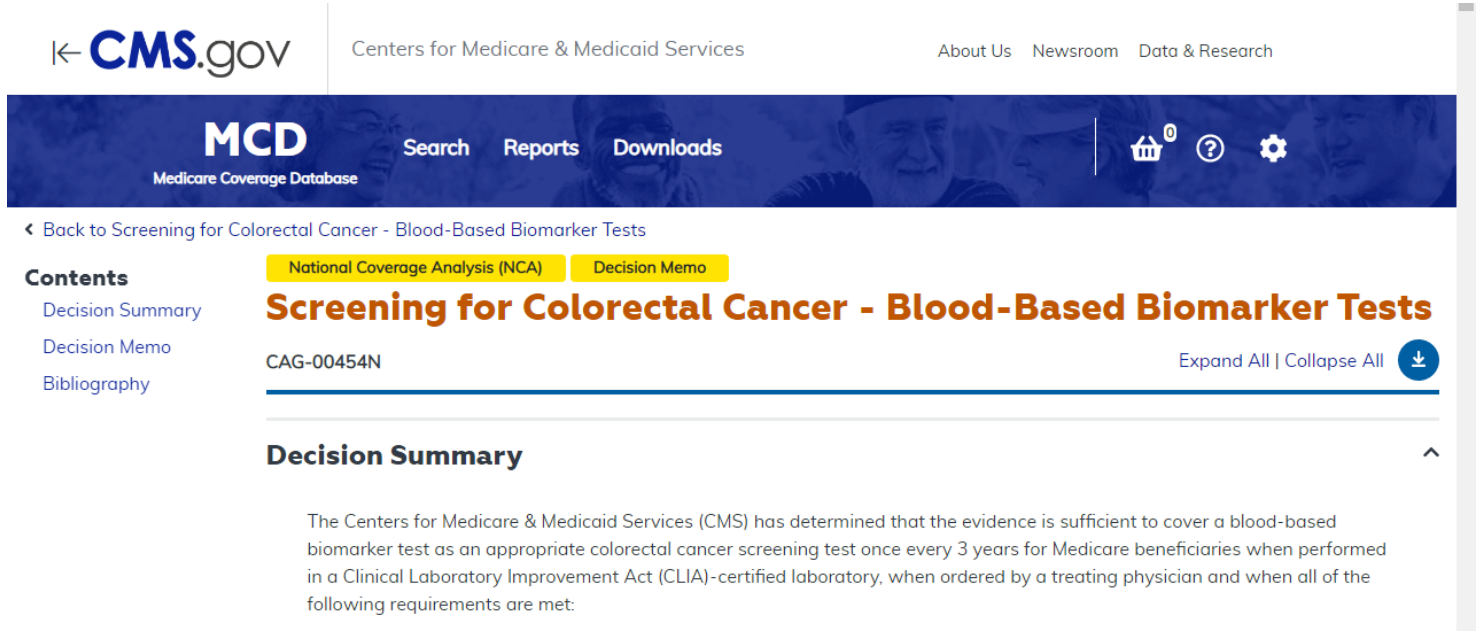
Shaukat A et al. Clinical Validation of a Circulating Tumor DNA-Based Blood Test to Screen for Colorectal Cancer. *JAMA*. 2025 1; 334(1):56-63.

Sensitivity by Stage of CRC



Shaukat A et al. Clinical Validation of a Circulating Tumor DNA-Based Blood Test to Screen for Colorectal Cancer. *JAMA*. 2025 1; 334(1):56-63.

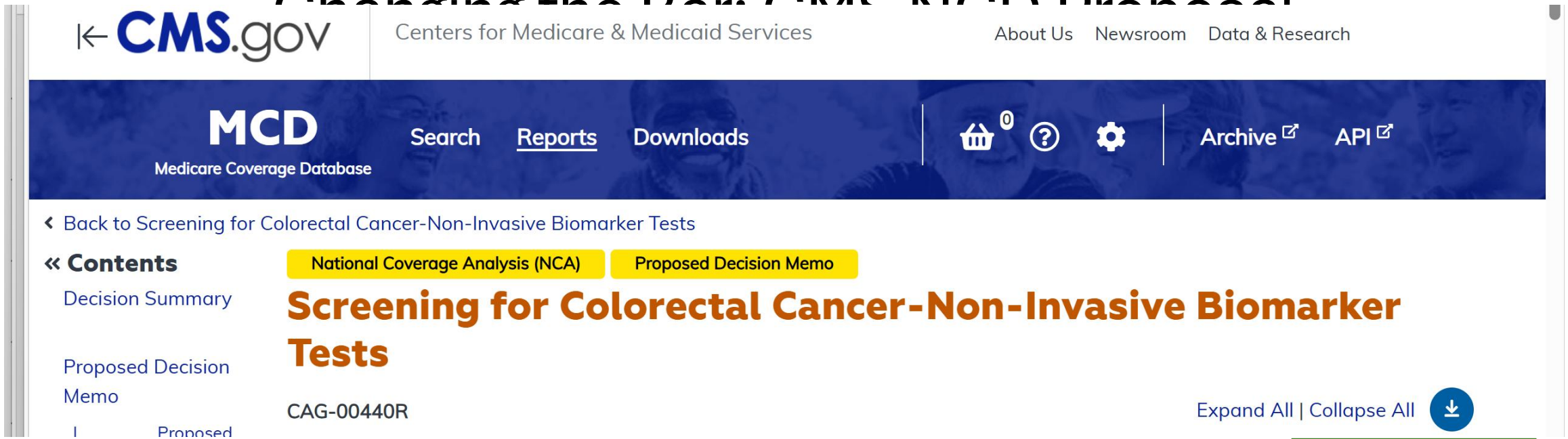
Setting the Bar: CMS National Coverage Decision



Sensitivity for CRC	74%
Specificity for CRC	90%
FDA approval	✓

Guardant and Freenome's blood tests meet and exceed

Changing the Bar: CMS NCD Proposal



	Test Performance Criteria 1	Test Performance Criteria 2
Sensitivity	≥ 90%	≥ 79%
Specificity	≥ 87%	≥ 90%

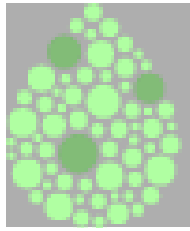
Guardant and Freenome's blood tests meet and exceed

NCA - Screening for Colorectal Cancer-Non-Invasive Biomarker Tests (CAG-00440R) - Proposed Decision Memo

Universal DIAGNOSTICS

INTERVENN

MAINZ BIOMED



CellMax Life

novigenix

natera™

Volition

New Kids on the Block

	Year	Test		N	CRC detection	AA detection
Stool	2023	Geneoscopy CRC-PREVENT	Mts-RNA test	8920; 45 and older	94% sensitivity 88% Specificity	46%
Stool	2024	Exact	Mts-DNA plus	20,176; 40 and older	94% sensitivity 91% Specificity	43%
Blood	2024	Guardant SHIELD	ctDNA BBT	7861; 45-84 year olds	83.1% sensitivity 89.6% Specificity	13.2%
Blood	2025	Freenome SimpleScreen	ctDNA BBT	27,010; 45-85 year olds	79.2% sensitivity 91.5% Specificity	12.5%

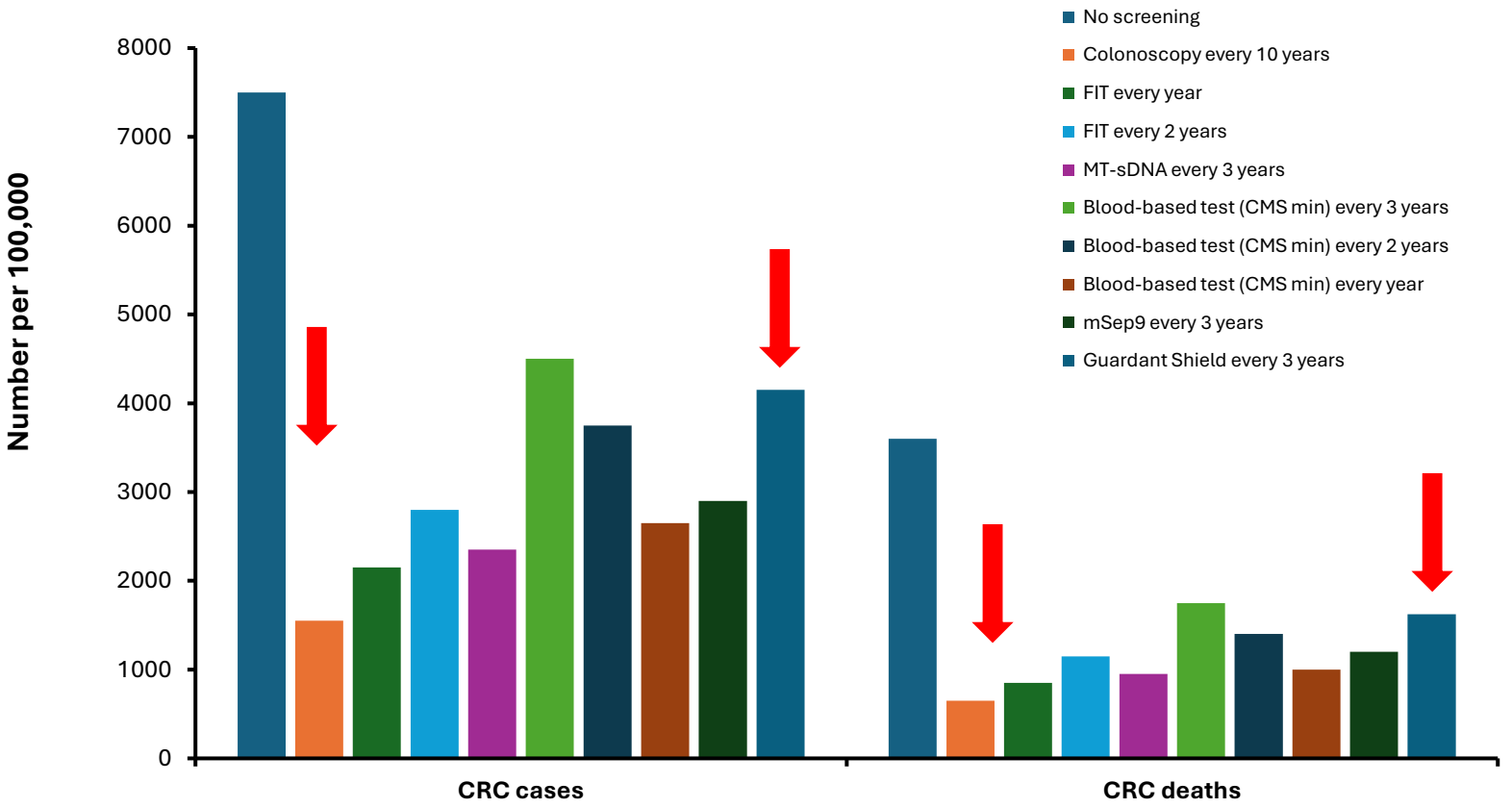
Barnell EK, Wurtzler EM, La Rocca J et al. Multitarget Stool RNA Test for Colorectal Cancer Screening. *JAMA*. 2023; 330(18):1760-1768; Imperiale T et al. *N Engl J Med*. 2024; 390:984-993; Chung D et al. *N Engl J Med*. 2024; 390:973-983; Shaukat A et al. *JAMA*. 2025; 334:56-63.

Practical Questions

- Repeat interval? → Company, experts, modelling
- Long term outcome--? Association with CRC incidence and mortality
- Follow up of false positives?
- Availability and cost?
- Adherence to the two steps?
- Could we worsen disparities?

Wang CP, Miller SJ, Shaukat A, Jandorf LH, Greenwald DA, Itzkowitz SH. Blood-based colorectal cancer screening: are we ready for the next frontier? *Lancet Gastroenterol Hepatol*. 2023; 8(10):870-872.

Modelling Comparison



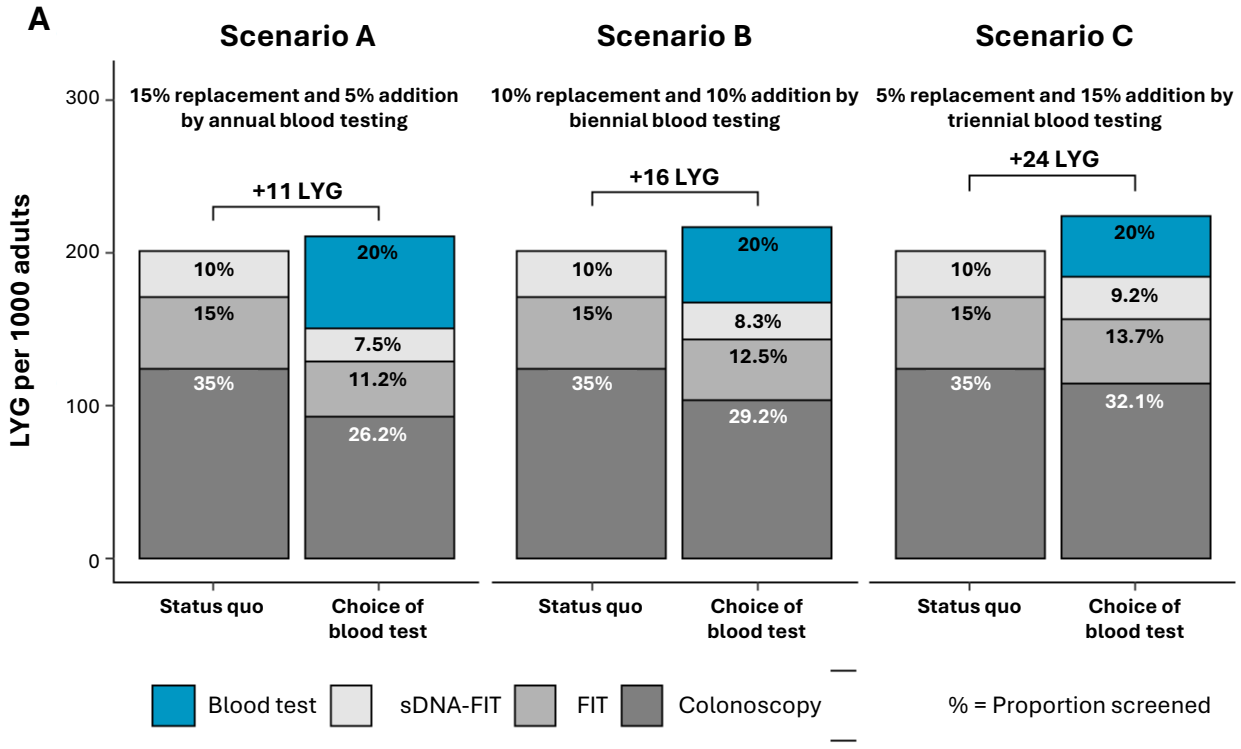
- Better than no Screening
- Inferior to Colonoscopy and stool test

Shaukat A, Ladabaum U, Kanth P, Lieberman D. AGA Clinical Practice Update on Current Role of Blood Tests for Colorectal Cancer Screening: Commentary. *Clin Gastroenterol Hepatol*. 2025 Aug; 23(9):1486-1491. doi: 10.1016/j.cgh.2025.04.003. Epub 2025 Apr 21. PMID: 40267995;
Ladabaum U et al. Comparative Effectiveness and Cost-Effectiveness of Colorectal Cancer Screening With Blood-Based Biomarkers (Liquid Biopsy) vs Fecal Tests or Colonoscopy. *Gastroenterology*. 2024; 167:378-391.

Comparative benefits, burdens, and harms of emerging blood-based tests for colorectal cancer screening

Reinier G.S. Meester, MS, PhD[*,1,2], Andrew J. Piscitello, MAT[3], Joseph A. Duimstra, PhD[4,5], Peter S. Liang, MD, MPH[6], Aasma Shaukat, MD, MPH[6], Theodore R. Levin, MD[7]

- Colonoscopy screening most LYG
- Stool test: 81%-88% of LYG for COL
- Blood test triennial: 57-72% of LYG for COL

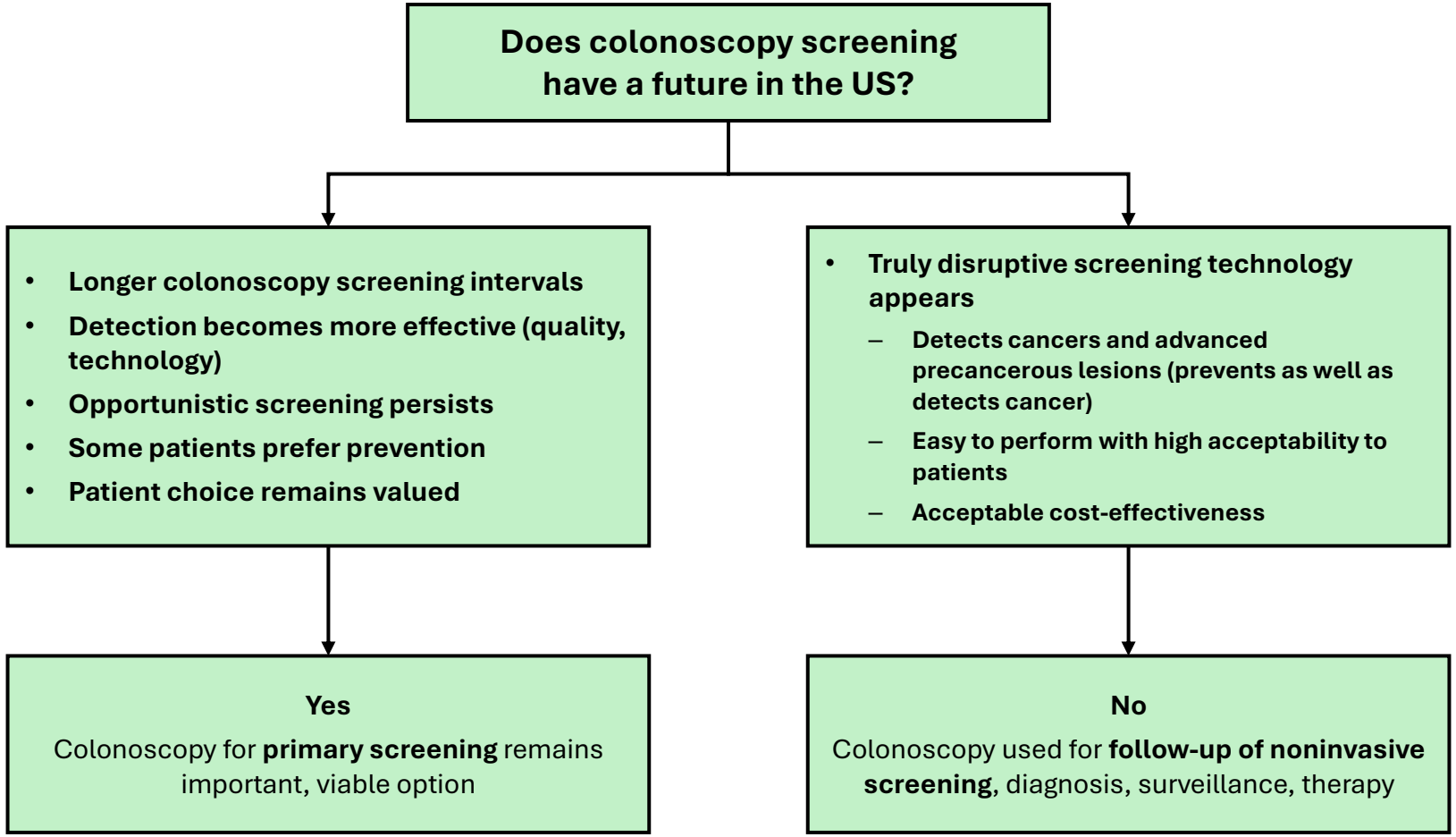


Reinier G S Meester, Andrew J Piscitello, Joseph A Duimstra, Peter S Liang, Aasma Shaukat, Theodore R Levin. Comparative benefits, burdens, and harms of emerging blood-based tests for colorectal cancer screening. *JNCI: Journal of the National Cancer Institute*. 2025; djaf277, https://doi.org/10.1093/jnci/djaf277.

CRC Screening Options

Modality	Sensitivity CRC	Sensitivity AA	Specificity	Invasive	USPSTF	Medicare
Colonoscopy	96%	95%	100%	Y	Y	Y
FIT	74%	24%	96%	N	Y	Y
mtsDNA stool	92%	42%	87%	N	Y	Y
mtsRNA stool	94%	46%	88%	N	-	Y
mtsDNA 2.0 stool	94%	43%	91%	N	-	Y
ctDNA blood	83.1%	13.2%	89.6%	N	-	Y
ctDNA blood	79.2%	12.5%	91.5%	N	-	-

Where Does Screening Colonoscopy Fit?



Douglas K. Rex, Uri Ladabaum, Joseph C. Anderson, Aasma Shaukat, Lynn F. Butterly, Jason A. Dominitz, Tonya Kaltenbach, Theodore R. Levin, Cesare Hassan. Does Screening Colonoscopy Have a Future in the United States? *Clinical Gastroenterology and Hepatology.* 2023; https://doi.org/10.1016/j.cgh.2023.05.034.

Multi Cancer Early Detection Tests: Pathway to Population Screening

Personal Genome Diagnostics

Medicine

Burning Rock

Biological Dynamics

20/20 GeneSystems

Precision Epigenomics

EarlyDiagnostics

Singlera Genomics

Biocept

QIAGEN

Epic Sciences

Exact Sciences

Guardant Health

GRAIL

Natera

Bluestar Genomics

Oncocyte

Delfi Diagnostics

Freenome

StageZero

Cardiff Oncology

LungLife AI

Resolution Bioscience

Elypta

Exosome Diagnostics

Adela

Caris Life Sciences

I think I'd like to have an MCED test, Doc, but which one?

MCEDs in the pipeline

			Targeted Cancers															
Company	Assay	Technology	Lung	CRC	Breast	Pancreas	Liver	Esophagus	Stomach	Ovary	Prostate	Bladder	Kidney	Uterus	H&N	Lymphoma	Leukemia	Plasma Cell
Adela Bio	adela	cfMeDIP-seq; cfDNA fragmentomics	■	■	■	■						■	■				■	
Biological Dynamics	Tr(ACE)	EV proteins; AI				■				■		■						
Bluestar Genomics	BluestarMCED	cfDNA 5hmC-seq; fragmentomics	■	■	■	■	■	■	■	■								
Burning Rock	OverC™	ELSA-seq	■	■		■	■	■		■								
Caris Life Sci	MI GPSai	cfDNA/cfRNA NGS; AI	■	■	■				■				■	■				
Delfi Dignostics	DELFI	cfDNA fragmentomics	■	■		■			■	■								
Early Diagnostics	cf Methyl-Seq	cfDNA mC-NGS	■	■			■		■									
Exact Sciences	CancerSEEK	cfDNA NGS; protein markers	■	■	■	■	■	■	■	■								
Freenome	FMBT	Multi-Omics/AI	■	■	■	■	■	■	■	■	■	■	■	■				
Grail	Galleri™	CpG-cfDNA NGS	■	■		■	■	■	■	■		■			■	■		■
LungLifeAI	LungLB	CTC FISH; Imaging AI	■		■		■						■					
Natera	Signatera™	cfDNA NGS; protein markers	■	■	■	■	■					■		■				
Precision Epigenomics	Sentinel-10™	CpG-cfDNA qPCR	■	■	■	■	■											
20/20 Gene Systems	oneTEST	circul. Cancer Ag's; AI	■	■	■	■	■				■							

https://prevention.cancer.gov/

Benefit and Benefit Harm Tradeoffs

- Imaging tests can be imperfect
- MCED-may lead to whole body scanning-risk for incidentalomas
- What to do about false positives
- Burden of confirming MCED test results can be very costly

- Critical gaps in current knowledge prevent reliably projecting the expected clinical impact of MCEDs
- No benefit for screening for many common cancers

Etzioni et al. JNCI J Natl Cancer Inst (2022) 114(3): djab168. doi: 10.1093/jnci/djab168
Woolf SH, Harris R. The Harms of Screening: New Attention to an Old Concern. *JAMA*. 2012;307(6):565–566. doi:10.1001/jama.2012.100

MCDs in trials

Test	Details of Technology	Special Considerations	Expected Completion
Blood-Based			
CancerGuard	Multi-cancer detection test for 8 common cancers, including CRC Detects circulating proteins and mutations in circulating tDNA	Has enrolled 6400 individuals Completed study: cancer free (n=3893), individuals with cancer, (n=727) ages 50 and older	♦ 2025
GRAIL	♦ Multi-cancer early detection test (breast, colorectal, pancreatic, lung and hematologic malignancies)	♦ Target enrollment 20,000 ♦ Not covered by insurance and the list price is $949 ♦ NHS-Galleri has enrolled 140,000 from 1.5M invited	♦ 2026

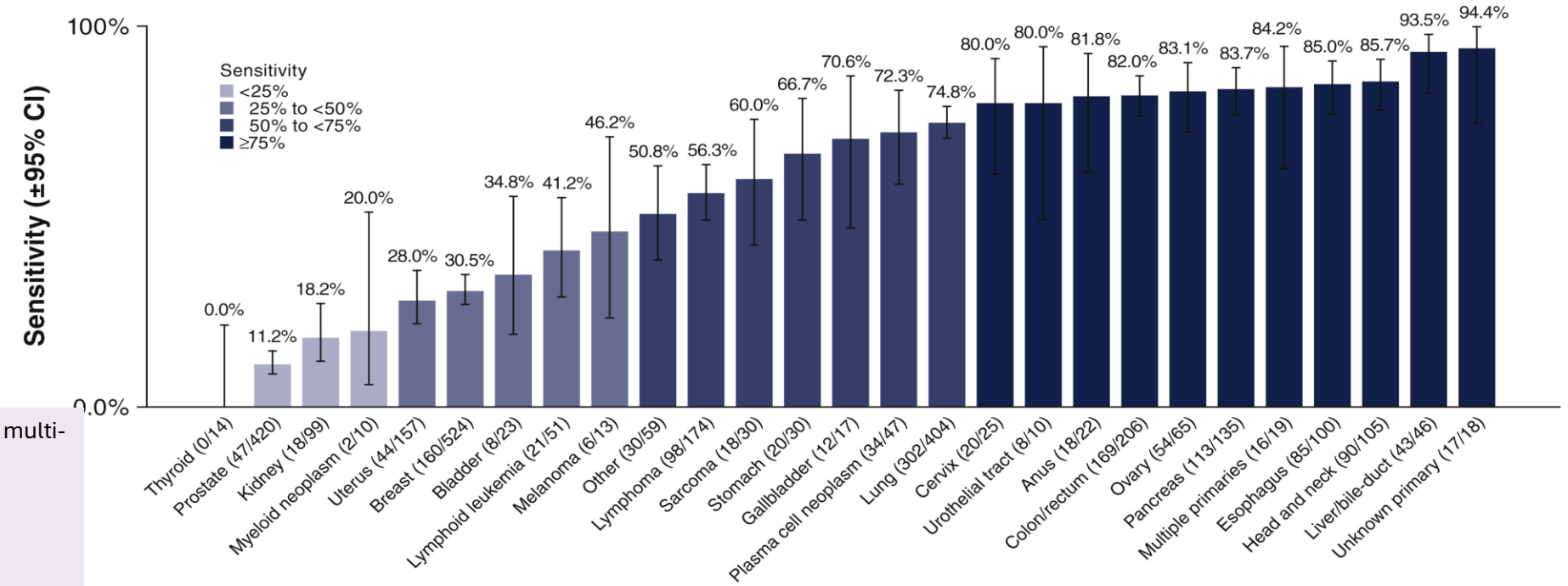
Neal RD, Johnson P, Clarke CA, Hamilton SA, Zhang N, Kumar H, Swanton C, Sasieni P. Cell-Free DNA-Based Multi-Cancer Early Detection Test in an Asymptomatic Screening Population (NHS-Galleri): Design of a Pragmatic, Prospective Randomised Controlled Trial. Cancers (Basel). 2022 Oct 1;14(19):4818. doi: 10.3390/cancers14194818. PMID: 36230741; PMCID: PMC9564213.
Clinicaltrials.gov

A

	Cancer	Non-cancer	Total
	2823	1254	4077
Test positive	1453	6	1459
Test negative	1370	1248	2618
	Sensitivity = 1453/2823 51.5% (49.6%-53.3%)	Specificity = 1248/1254 99.5% (99.0%-99.8%)	

Two-sided 95% Wilson confidence intervals were calculated.

B



Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set.Klein, E.A. et al.Annals of Oncology, Volume 32, Issue 9, 1167 - 1177

- 150k 50+ NHS participants enrolled since 2022
- Concerns on process, results, resource use
- Interim analysis 2025

BMJ 2024; 386 doi: https://doi.org/10.1136/bmj.q1706 (Published 07 August 2024)

- Primary endpoint of statistically significant Stage III-IV reduction was not observed
- Galleri +standard of care screening resulted in a clinically meaningful reduction in Stage IV diagnoses across 12 deadly cancers

GRAIL Announces U.S. Sales Force Expansion Based on Strong NHS-Galleri and PATHFINDER 2 Trial Results

https://grail.com/press-releases/ Feb 19, 20206

These tests are in market now, as LDTs

- Galleri being sold for $949 per test
- CancerGuard sold for $689 per test (PET-CT extra)
- Not covered by Insurance

- Randomized trials are needed,—but these trials are $$$, require vast sample sizes and take a long time

- It is likely release of these tests into the market will get ahead of the trials

Published Nov 4, 2021

San Francisco Rapper & Cannabis Entrepreneur, Berner, 40, Shares That His Cancer Surgery 'Went Well,' But 'We Still Have a Battle to Fight'

Berner revealed last month that doctors discovered his cancer after a series of blood tests.

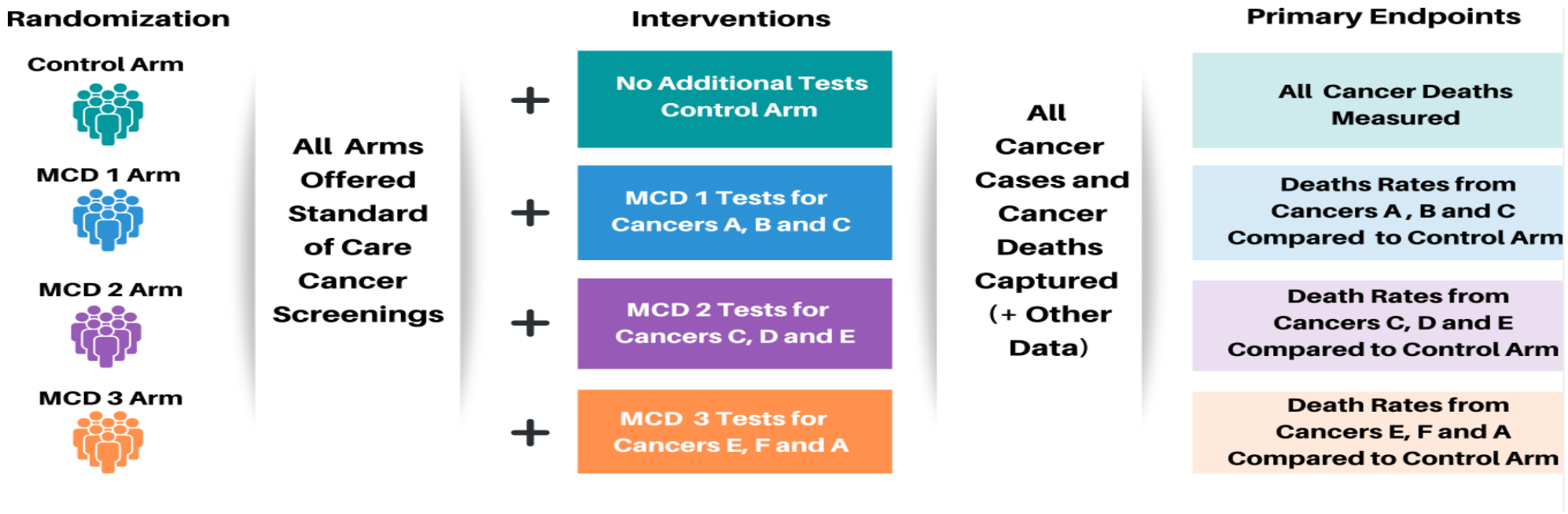
Sydney Schaefer

Details

Do Blood Tests to Detect Cancer Actually Work?

Initiatives underway

- NCI Cancer Screening Research Network
- VANGAURD study being planned



https://prevention.cancer.gov/major-programs/cancer-screening-research

Follow up Colonoscopy completion

HEDIS

NCQA Advances Development of a New HEDIS® Measure for Colorectal Cancer Screening Follow-Up

March 4, 2026 · NCQA Communications

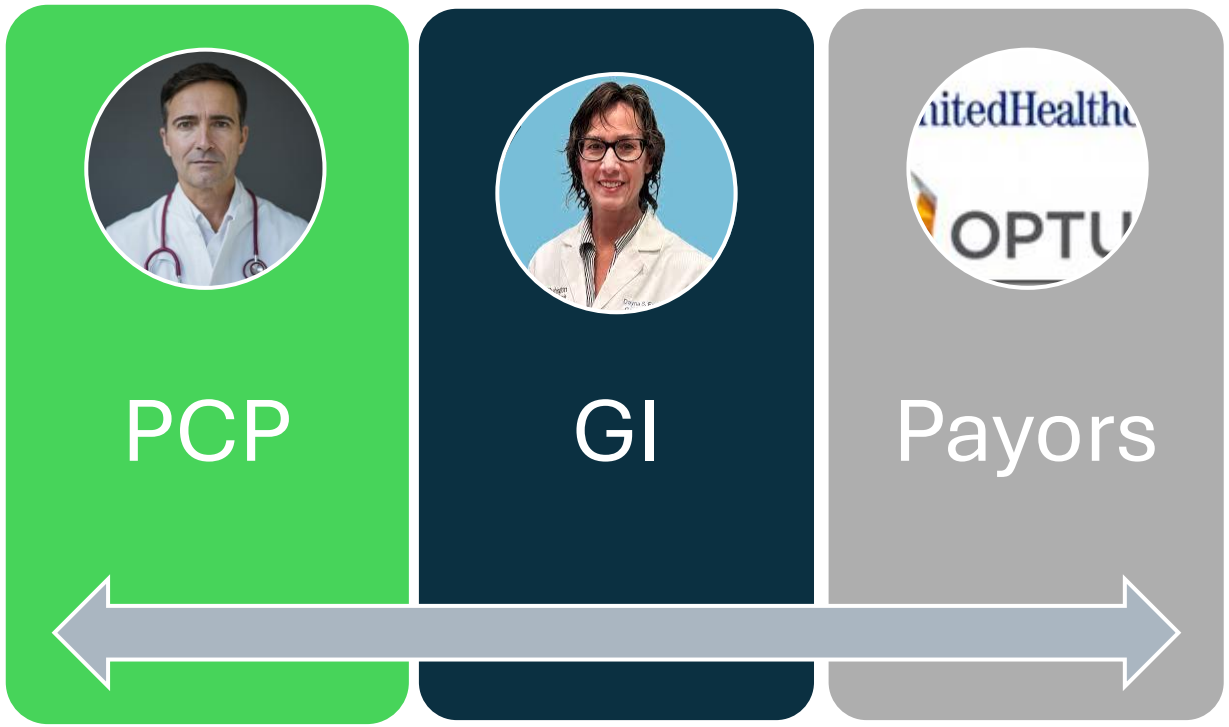
In recognition of Colorectal Cancer Awareness Month, we are sharing an update on our ongoing efforts to develop a new HEDIS® measure for colorectal cancer screening follow-up.

Follow up colonoscopy completion after abnormal stool test:

80% at 6 months

Public Comments - NCQA

Changing Landscape



- Educate payors and public
- Easy access to colonoscopy
- Effort at scheduling referrals
- High quality exams
- Community outreach
- Advocate for patients w payors

GI's Role in Changing Landscape

- Proficient at polypectomy
- Scheduling flexibility
- Access for all patients referred
- Referral follow through
- Metric driven:
  - ADR
  - Follow up colonoscopy completion rates after abn stool test
  - Excellent preps at Unit level
- Public education/outreach
- Visible advocacy

Summary

- New Stool and Blood based tests are moving into the market
- Guardant Shield is first blood based test FDA and CMS approved
- Consumer interest and marketing may get ahead of scientific evidence
- Application and implementation needs to careful evaluation

Thank you!

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