Blood-based biomarkers (liquid biopsy) to screen for colorectal neoplasia: Stanford MOSAIC model

WEO CRC SC, North America 2024

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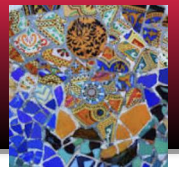
Agenda

- Modeling for AGA Workshop, and publication in Gastroenterology
- Modeling since NEJM March 2024 publications:
  - cell-free blood DNA (cf-bDNA, Guardant Shield)
  - next-generation multi-target stool DNA (ng-MT-sDNA, Cologuard, Exact Sciences)

MOSAIC



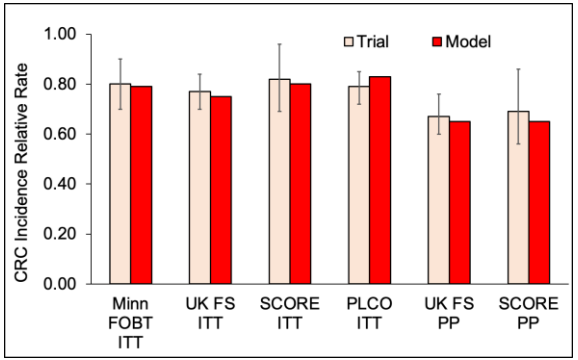
- **M**odel **o**f **S**creening **a**nd Surve**i**llance for **C**olorectal Cancer (MOSAIC)
- Refinement from our previously published model (validated vs. screening RCTs)
- MOSAIC v2023.1
  - Calibration to contemporary polyp prevalence
  - Validation to metachronous CRC incidence and death after colonoscopy (normal, LRA, HRA)

MOSAIC model

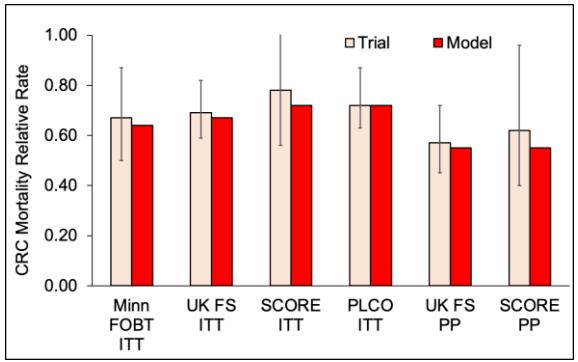
NA-P = Non-advanced polyp
APL = Advanced precancerous lesion
CRC-L = localized CRC
CRC-R = regional CRC
CRC-D = distant CRC
Sx = symptoms
Rx = treatment

Validations: 4 RCTs and 4 post-colonoscopy cohorts

CRC Incidence RR screen vs. not



CRC Death RR screen vs. not



Sharaf and Ladabaum, Am J Gastroenterol 2013;108:120

Model matches RCTs ITT and PP

Ladabaum et al, Gastroenterology 2024; In press

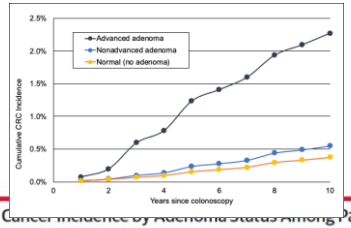
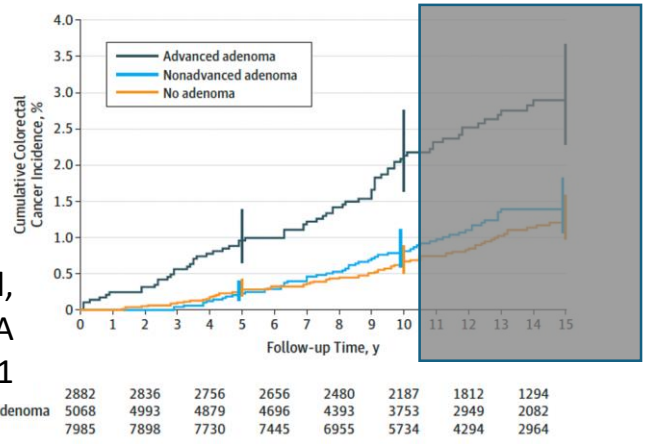


Figure 2. Cumulative Colorectal Cancer Incidence by Adenoma Status Among Participants Aged 55 to 74 Years Enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Randomized Clinical Trial

Click et al, JAMA 2018;319:2021



- ALSO:
  - ✓ He et al, Gastro 2020;158:852
  - ✓ Lee et al, Gastro 2020;158:884
  - ✓ Loberg et al, NEJM 2014;371:9

CMS National Coverage Determination

Table 5. Point Sensitivities and Specificities of Non-invasive CRC screening tests (compared to colonoscopy)

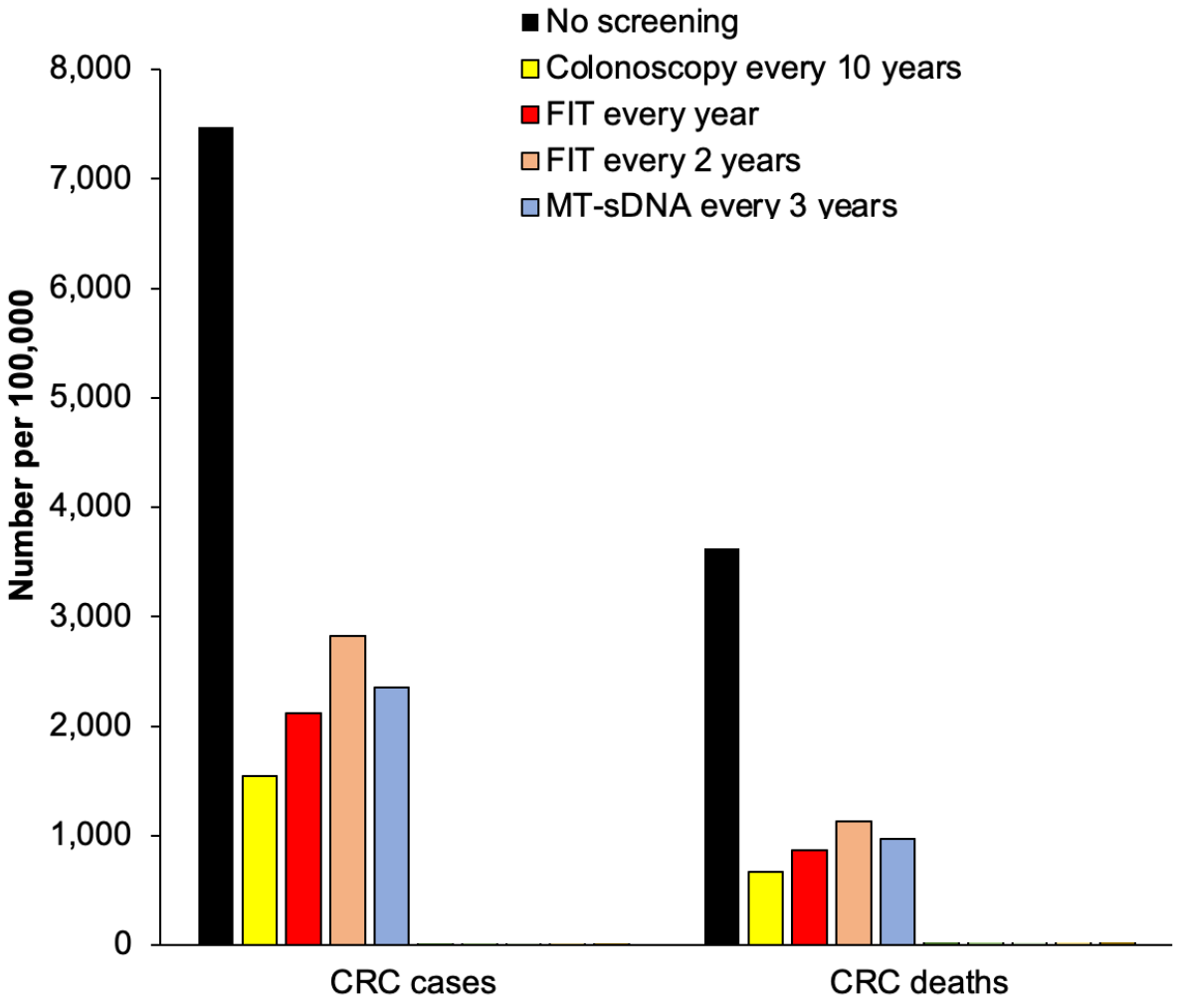
	Sensitivity (%)	Specificity (%)
FIT	74	96
Stool DNA test	92	90
Epi proColon® test	72	81
Proposed blood-based biomarker (use lower number from among covered tests, Table 4)	*74*	*90*

CMS Coverage Decision, 2020

Comparative Effectiveness and Cost-Effectiveness of Colorectal Cancer Screening With Blood-Based Biomarkers (Liquid Biopsy) vs Fecal Tests or Colonoscopy

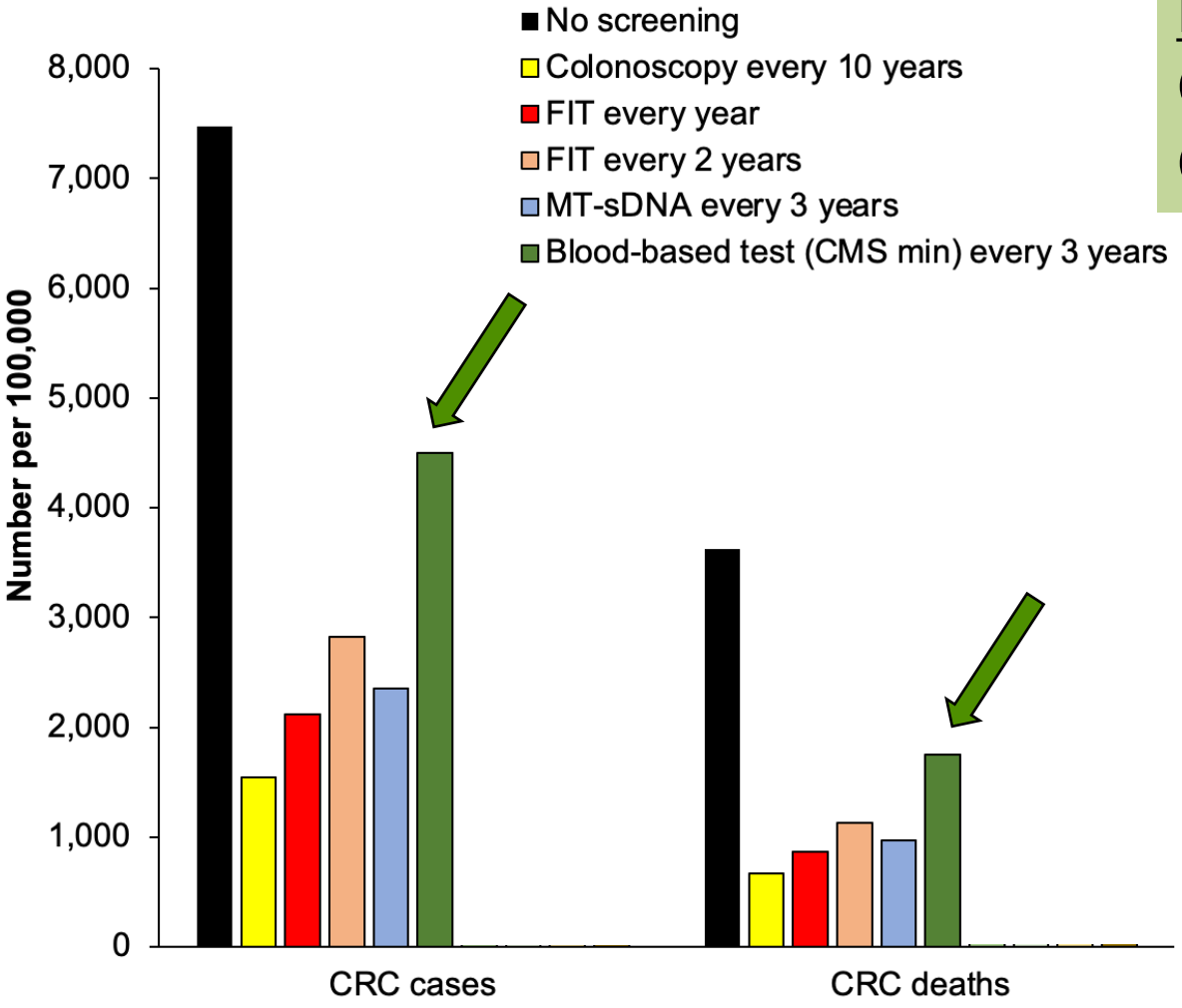
Uri Ladabaum,[1,2] Ajitha Mannalithara,[1,2] Yingjie Weng,[2,3] Robert E. Schoen,[4] Jason A. Dominitz,[5,6] Manisha Desai,[2,3] and David Lieberman[7]

Ladabaum et al, Gastroenterology 2024; In press



Colonoscopy, FIT, MT-sDNA

Ladabaum et al, Gastro 2024; In press

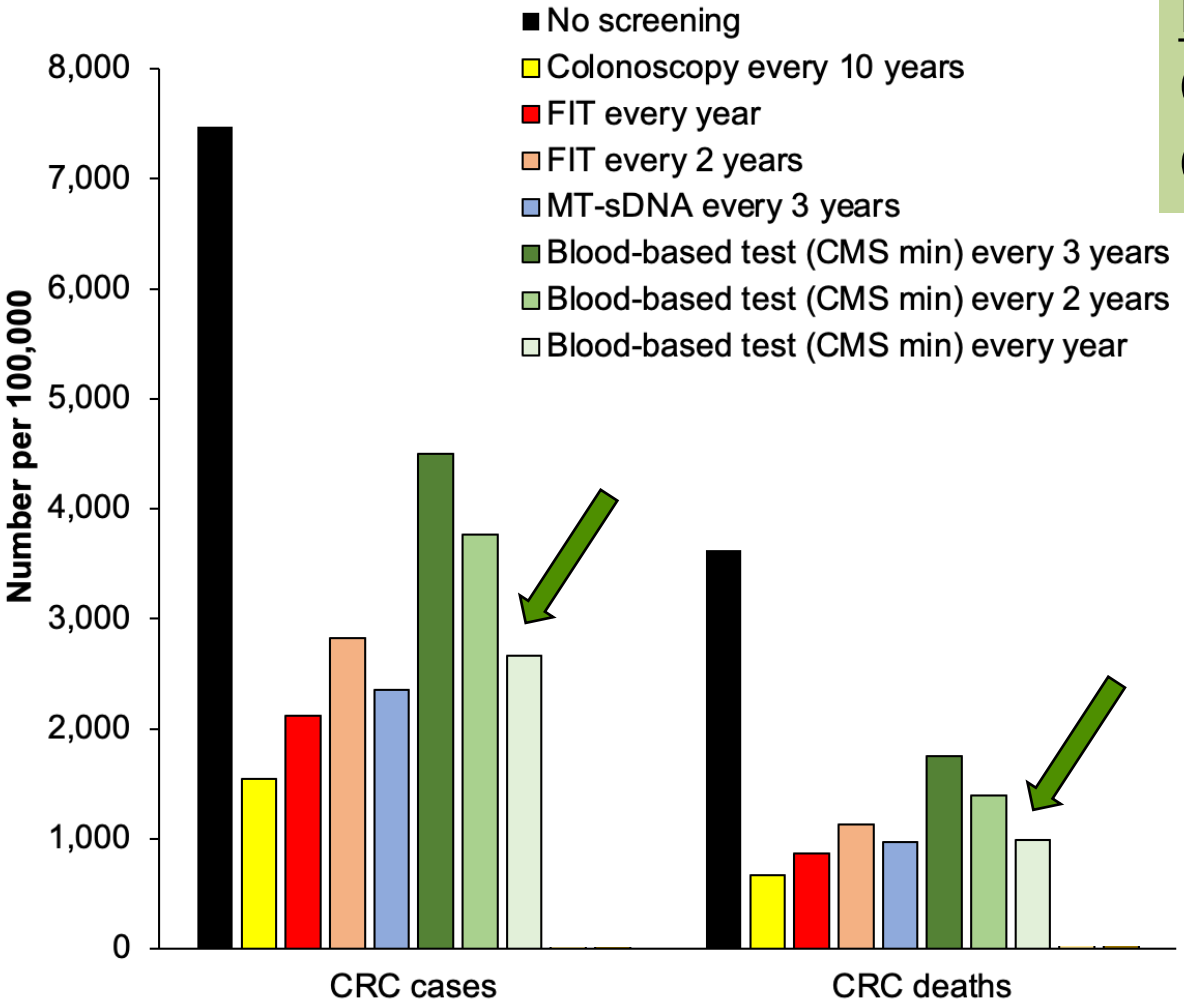


Blood test (CMS min):
CRC sensitivity 74%
CRC specificity 90%

CMS min every 3y
is less effective than

Colonoscopy, FIT,
MT-sDNA

Ladabaum et al, Gastro 2024; In press

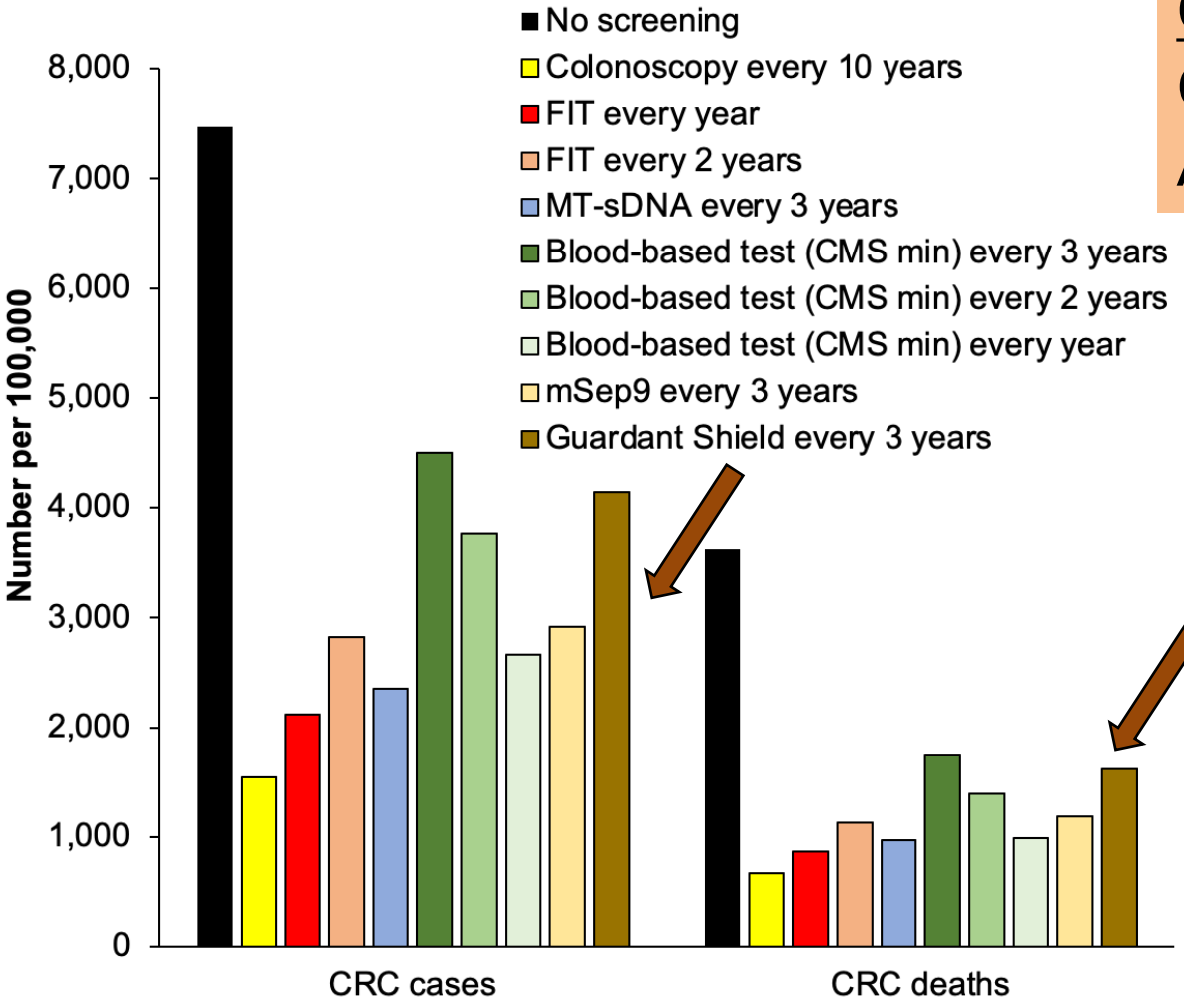


Blood test (CMS min):
CRC sensitivity 74%
CRC specificity 90%

CMS min YEARLY approaches

MT-sDNA

Ladabaum et al, Gastro 2024; In press

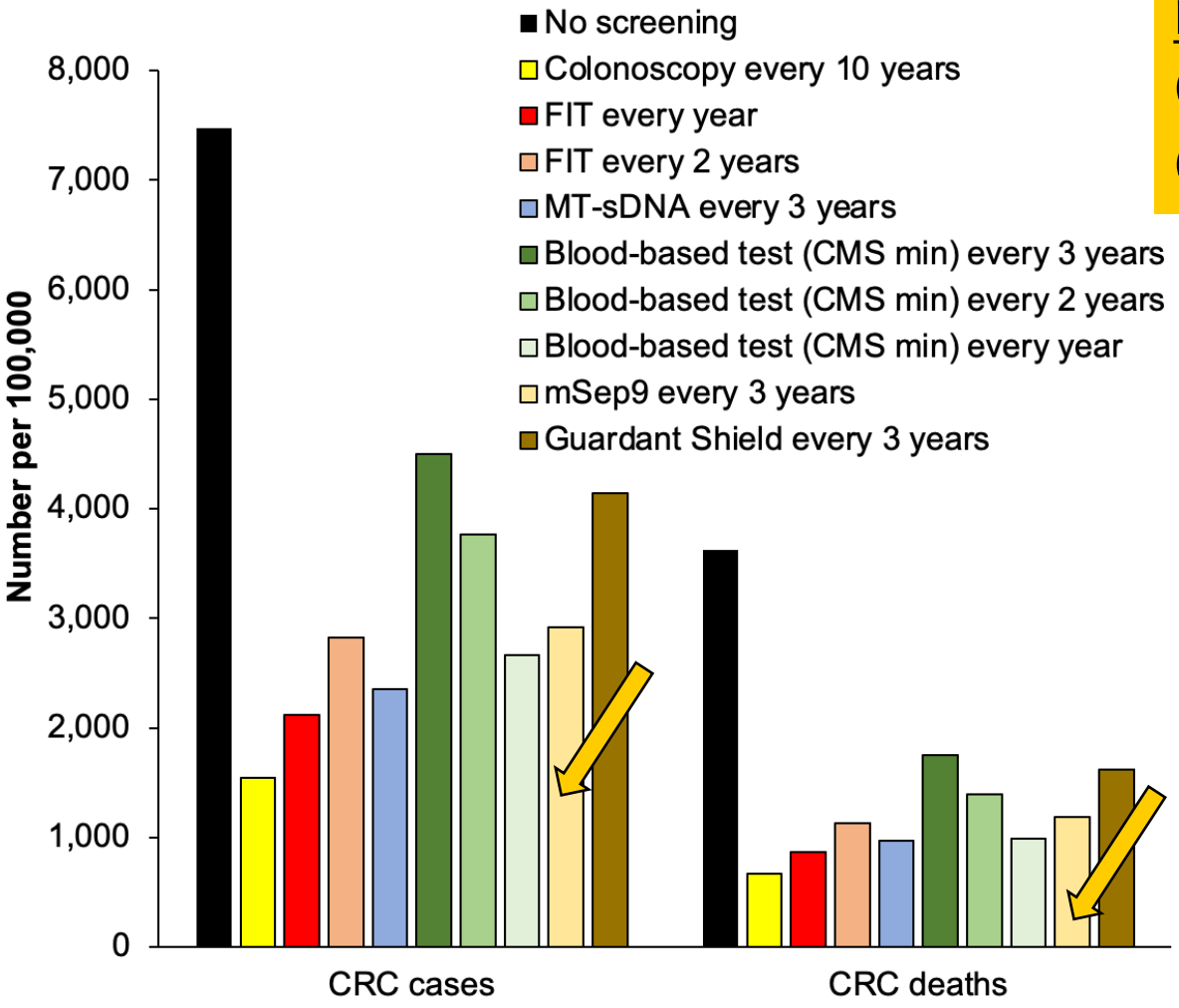


Guardant Shield:
CRC sensitivity 83%
APL sensitivity 13%

Shield every 3y is less effective than

Colonoscopy, FIT, MT-sDNA

Ladabaum et al, Gastro 2024; In press

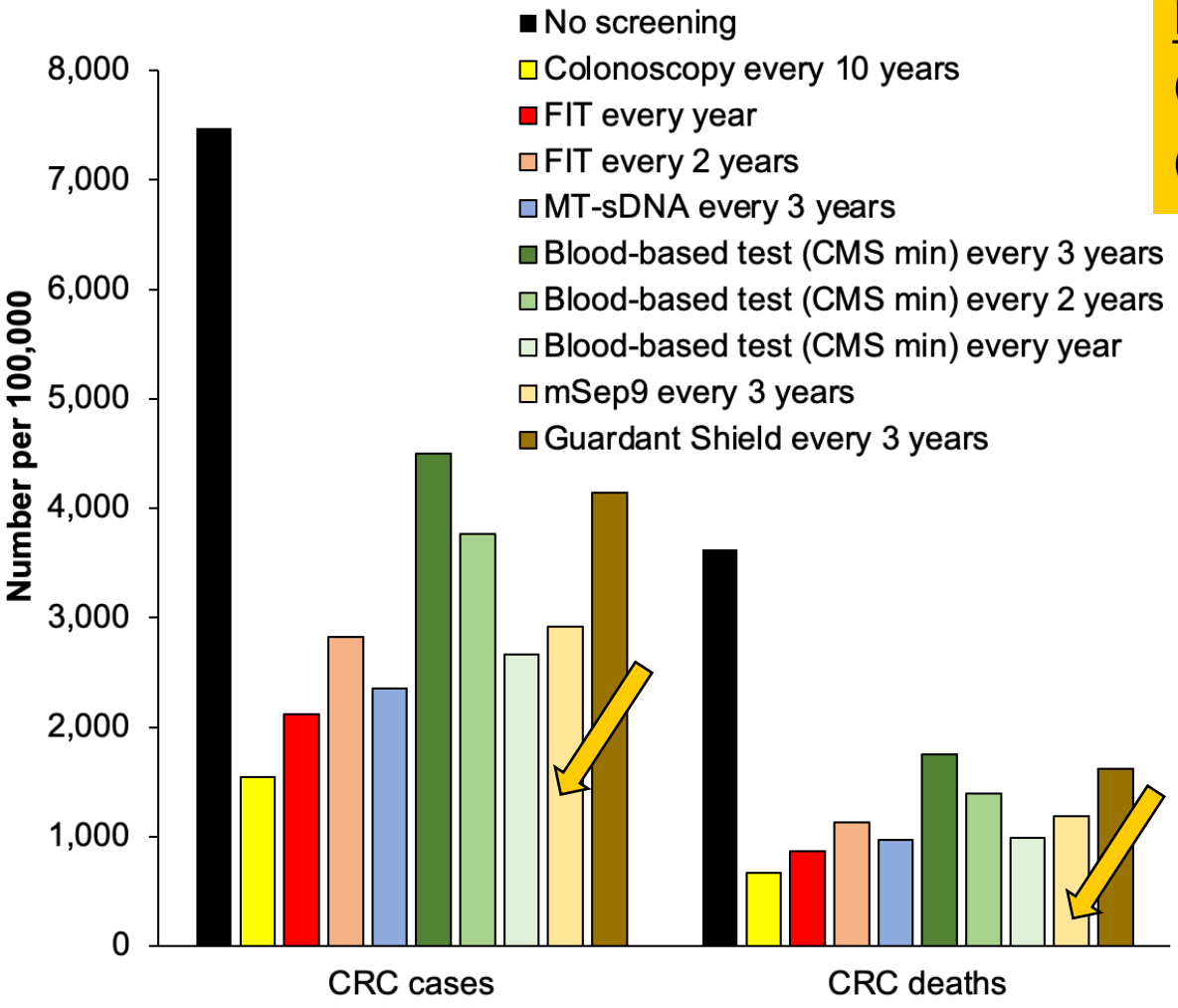


mSeptin9:
CRC sensitivity 64%
CRC specificity 79%

mSeptin9 q3y is more effective than

CMS min, Shield q3

Ladabaum et al, Gastro 2024; In press



mSeptin9:
CRC sensitivity 64%
CRC specificity 79% *

mSeptin9 q3y is more effective than

CMS min, Shield q3

** non-specificity → "detects" APL*

Ladabaum et al, Gastro 2024; In press

Participation relative to annual FIT

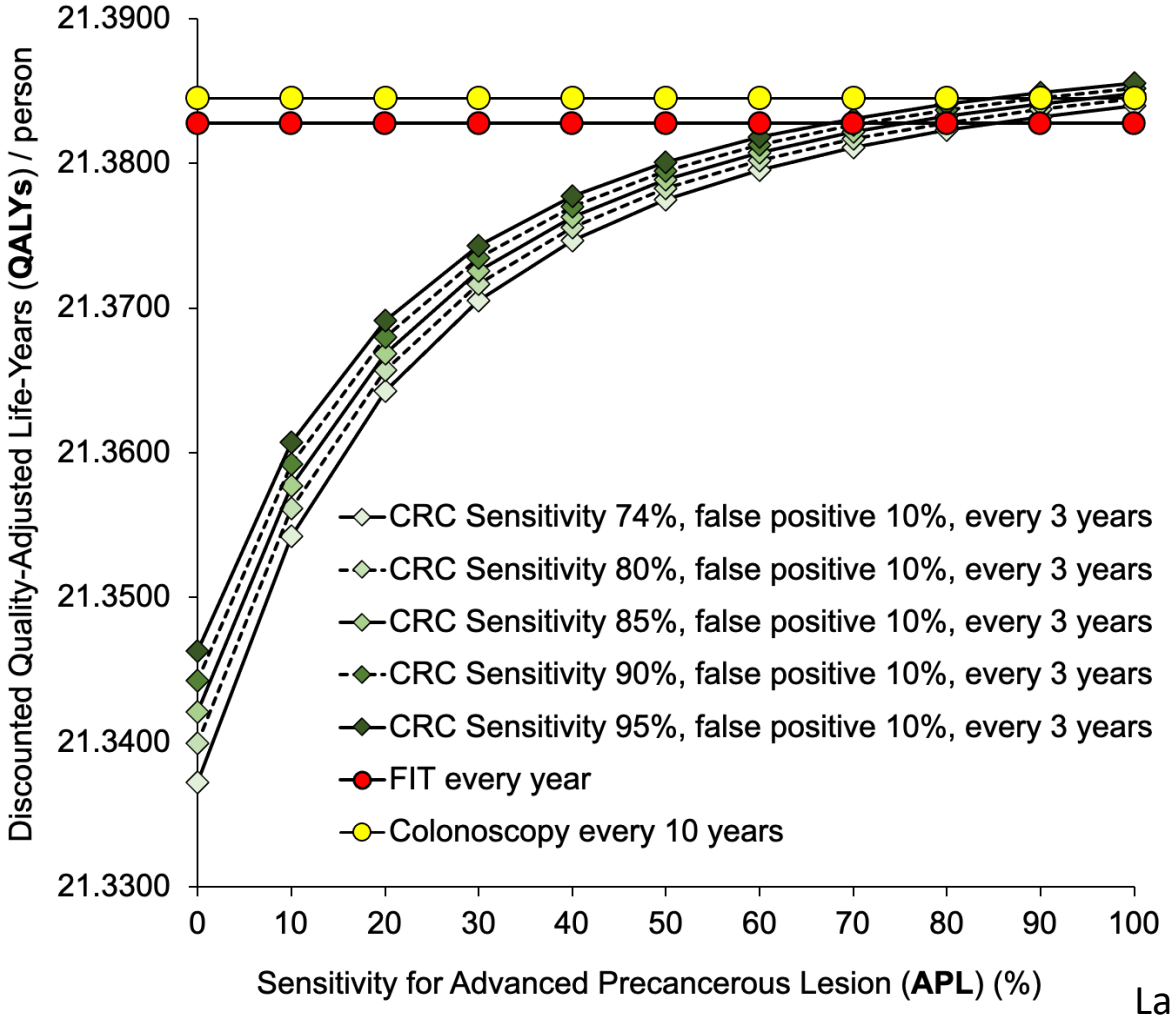
- CMS_{min} (sens 74%, spec 90% for CRC) q3 years matches annual FIT's results for:
  - CRC prevention at 1.8x participation
  - CRC death prevention at 1.5x participation
  - QALYs gained at 1.4x participation

Ladabaum et al, Gastro 2024; In press

MOST IMPORTANT MESSAGE

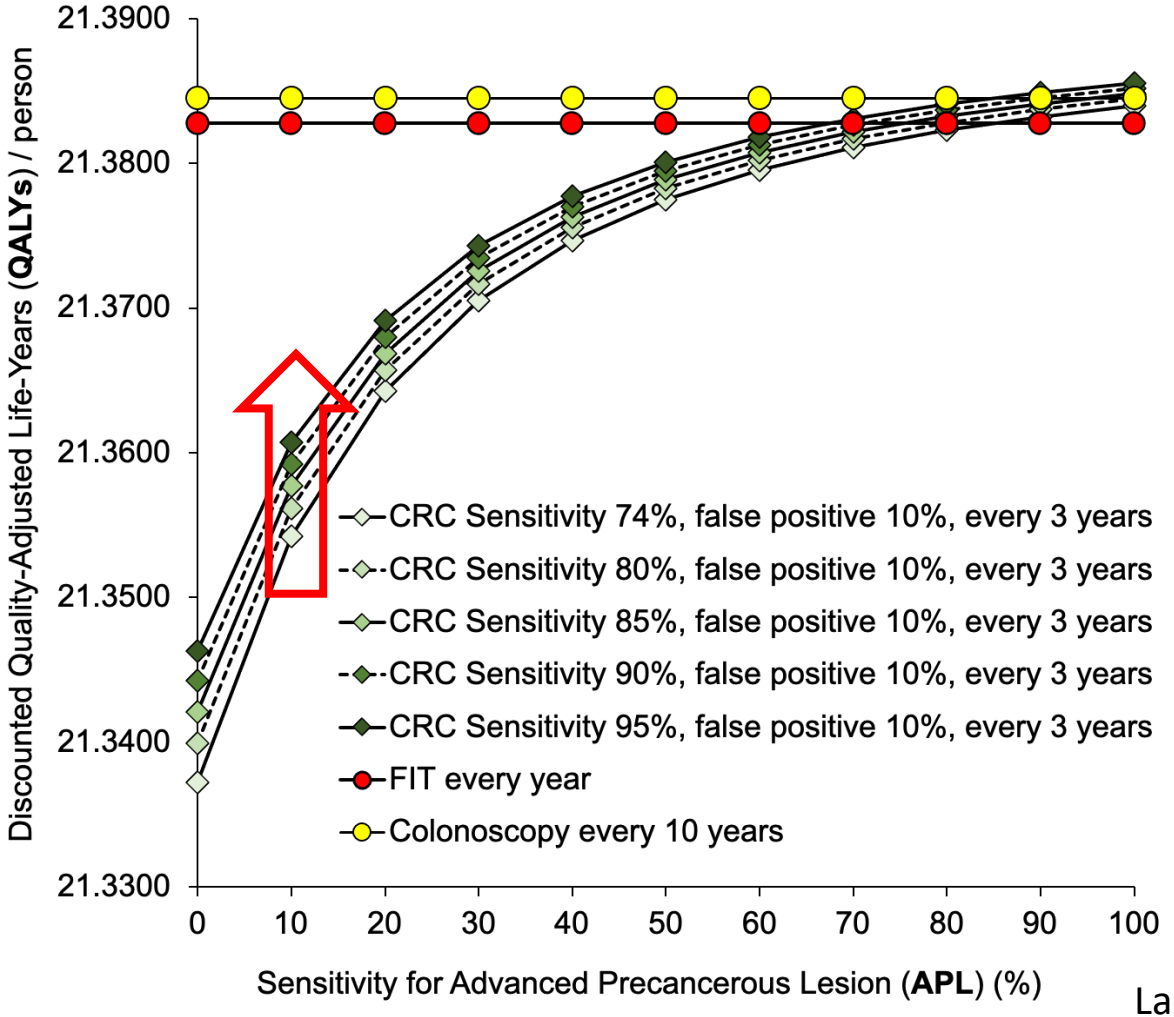
- CMS_{min} that captures unscreened "always-refusers" for stool tests or colonoscopy:
  - ***improves outcomes***
  - *$28,500/QALY gained (if same cost as MT-sDNA)*
- CMS_{min} that substitutes for effective stool tests or colonoscopy:
  - ***worsens outcomes***

Ladabaum et al, Gastro 2024; In press



Sensitivity for Advanced Precancerous Lesion (APL) is critical!

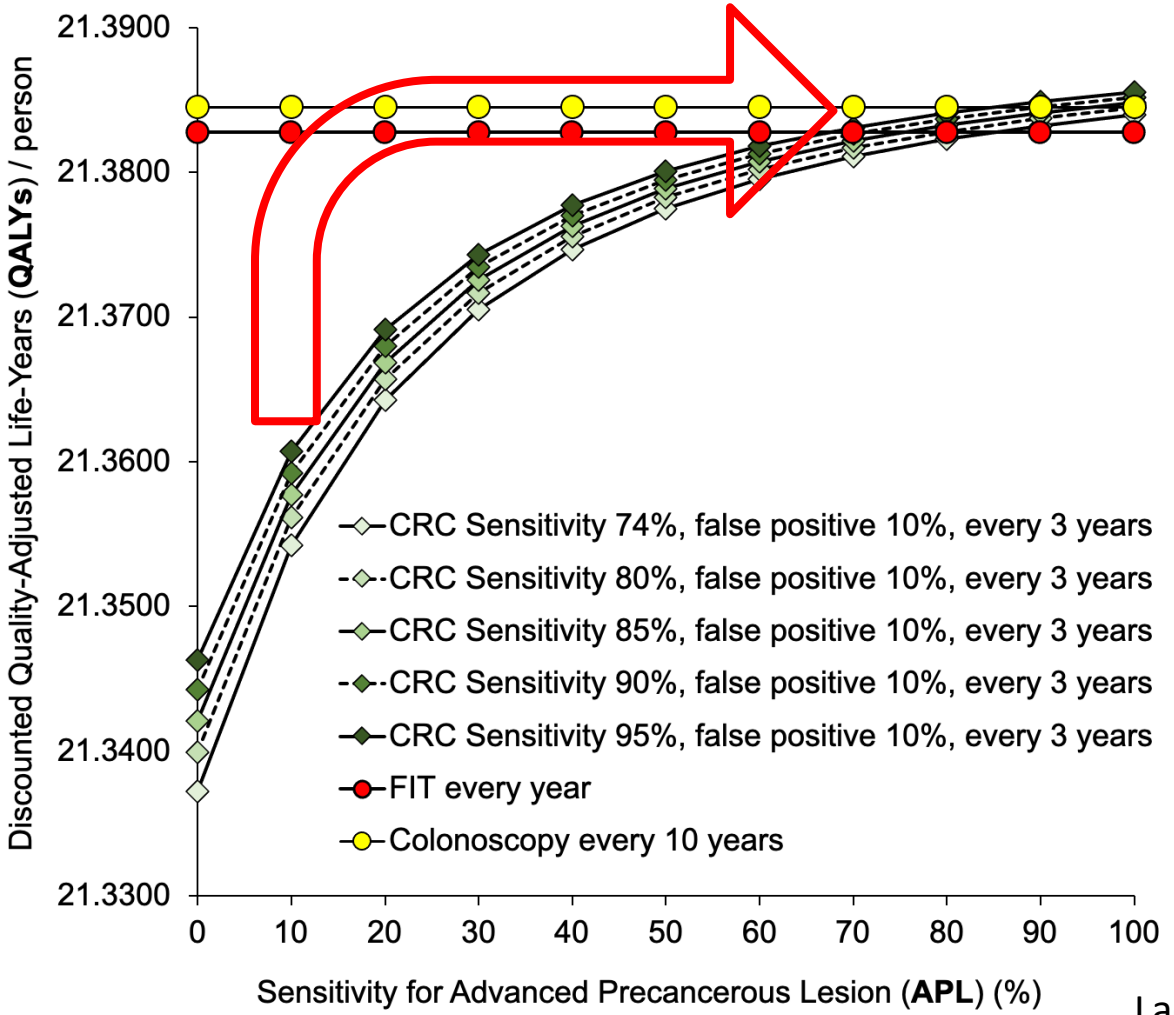
Ladabaum et al, Gastro 2024; In press



Sensitivity for Advanced Precancerous Lesion (APL) is critical!

Increasing CRC sensitivity has modest impact

Ladabaum et al, Gastro 2024; In press



Sensitivity for Advanced Precancerous Lesion (APL) is critical!

Increasing **APL sensitivity** has large impact

Ladabaum et al, Gastro 2024; In press

A paradigm-changing blood test

- CRC sensitivity 90%
- APL sensitivity 70-80%
- False positive rate 10% (90% “specificity”)
- Every 3 years
- Test cost $120 - $140

Ladabaum et al, Gastro 2024; In press

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2024 VOL. 390 NO. 11

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.

Chung et al, NEJM 2024; 390:11

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Next-Generation Multitarget Stool DNA Test for Colorectal Cancer Screening

Thomas F. Imperiale, M.D., Kyle Porter, M.A.S., Julia Zella, Ph.D., Zubin D. Gagrat, B.S., Marilyn C. Olson, Ph.D., Sandi Statz, M.S., Jorge Garces, Ph.D., Philip T. Lavin, Ph.D., Humberto Aguilar, M.D., Don Brinberg, M.D., Charles Berkelhammer, M.D., John B. Kisiel, M.D., and Paul J. Limburg, M.D., for the BLUE-C Study Investigators*

Imperiale et al, NEJM 2024; 390:11

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)

Chung et al, NEJM 2024; 390:11

Table 1. Sensitivity and Specificity of the Next-Generation Multitarget Stool DNA Test and the Commercial FIT.*

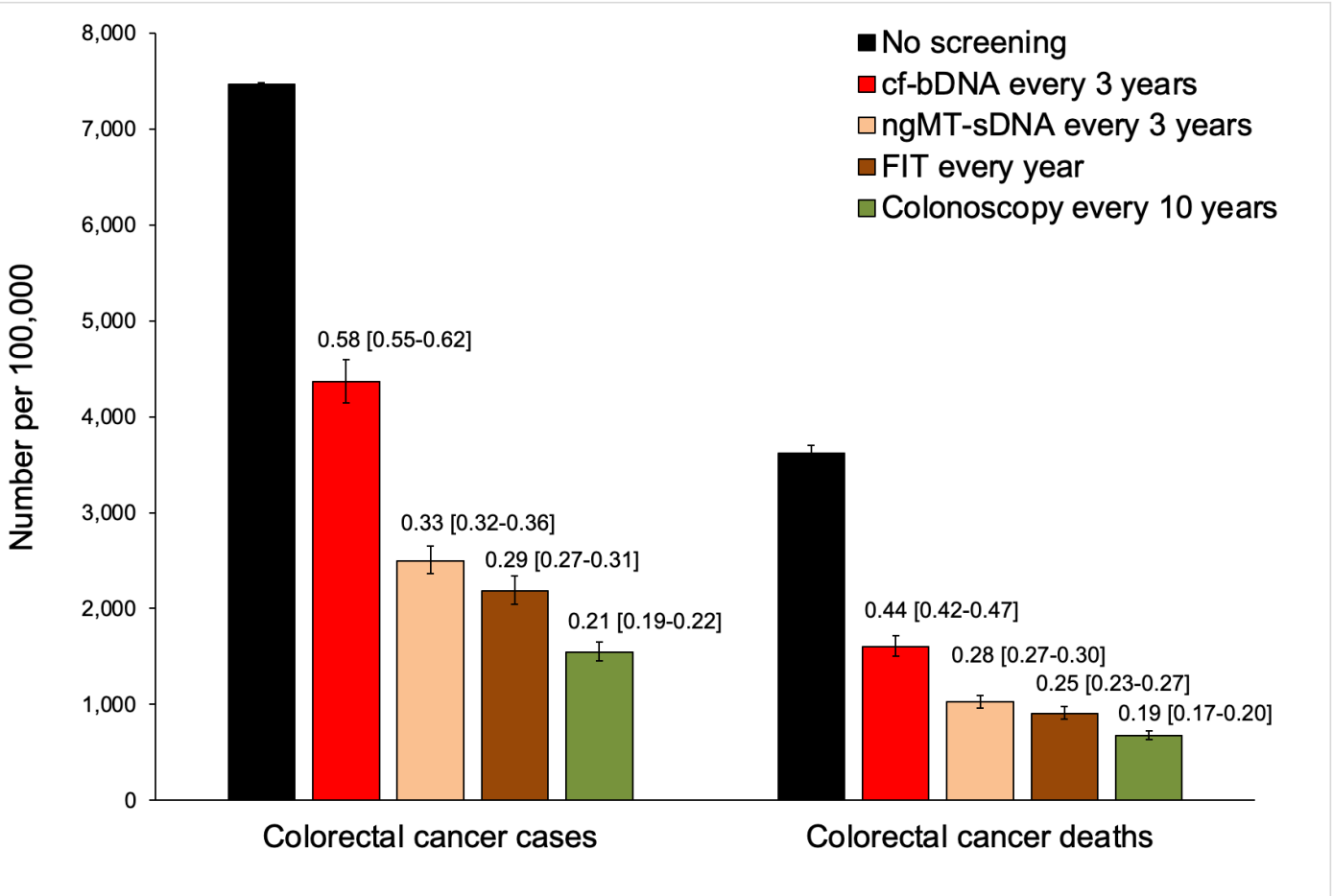
Variable	Colonoscopy (N = 20,176)	Next-Generation Multitarget Stool DNA Test (N = 20,176)		FIT (N = 20,176)	
	No. of Participants	No. of Results	Assessment (95% CI) %	No. of Results	Assessment (95% CI) %
Sensitivity					
Colorectal cancer					
Any	98	92	93.9 (87.1–97.7)†	66	67.3 (57.1–76.5)
Stage I, II, or III‡	82	76	92.7 (84.8–97.3)	53	64.6 (53.3–74.9)
Advanced precancerous lesions	2,144	931	43.4 (41.3–45.6)†	500	23.3 (21.5–25.2)
High-grade dysplasia	114	85	74.6 (65.6–82.3)	54	47.4 (37.9–56.9)
Specificity					
Advanced neoplasia§	17,934	16,245	90.6 (90.1–91.0)	16,997	94.8 (94.4–95.1)¶
Nonneoplastic findings or negative colonoscopy‖	10,961	10,156	92.7 (92.2–93.1)	10,492	95.7 (95.3–96.1)
Negative colonoscopy**	7,510	7,012	93.4 (92.8–93.9)	7,207	96.0 (95.5–96.4)

Imperiale et al, NEJM 2024; 390:11

MOSAIC's predictions (probabilistic)

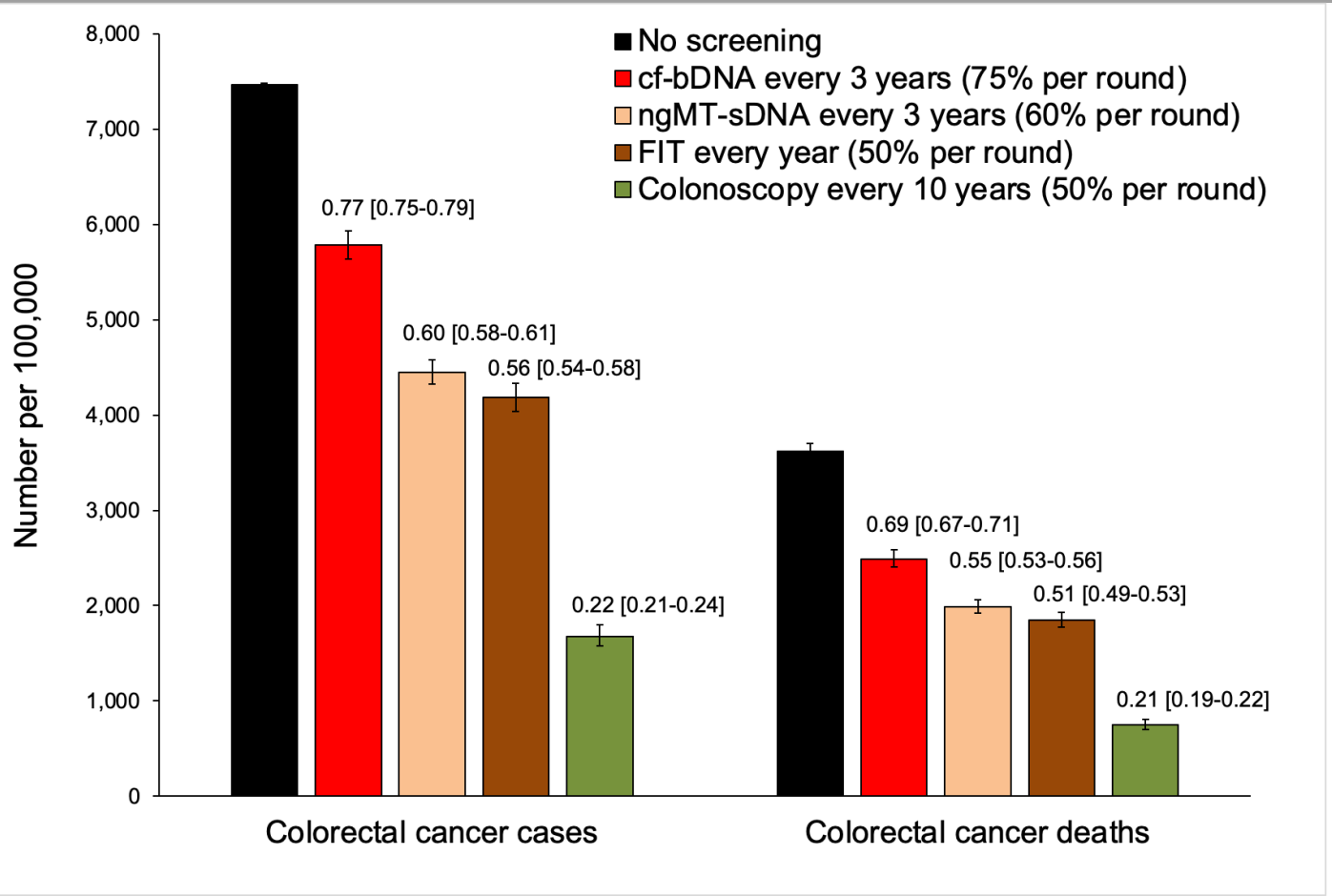
- Account for decreases in specificity for cf-bDNA and ngMT-sDNA as age increases
- Account for increases in APL detection for cf-bDNA and ngMT-sDNA as age increases
- Reflect uncertainty in test performance characteristics (distributions, 95% CIs)
- Compare to FIT CRC sensitivity 67% (not 74%)

Perfect participation and colonoscopy f/up



Numbers above bars are Relative Risk vs. no screening (mean [95% range of 10,000 iterations])

Differential per-round participation, colo f/up 60%



Numbers above bars are Relative Risk vs. no screening (mean [95% range of 10,000 iterations])

Summary

- CMS_{min}: probably highly effective and cost-effective in persons who refuse stool tests or colonoscopy
- CMS_{min} (every 3 years) *should not substitute for stool tests or colonoscopy*
- Guardant Shield resembles CMS_{min}
- APL sensitivity should be a priority for test developers
- Participation and test cost are key variables