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Higher assumed adherence to blood-based vs stool-based screening can compensate for potential lower advanced adenoma sensitivity

A model-based analysis

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Disclosure information

Reinier G.S. Meester, PhD

- I disclose the following financial relationship:
  - Principal of Health Economics & Modeling, Freenome Holdings, Inc., San Francisco, CA

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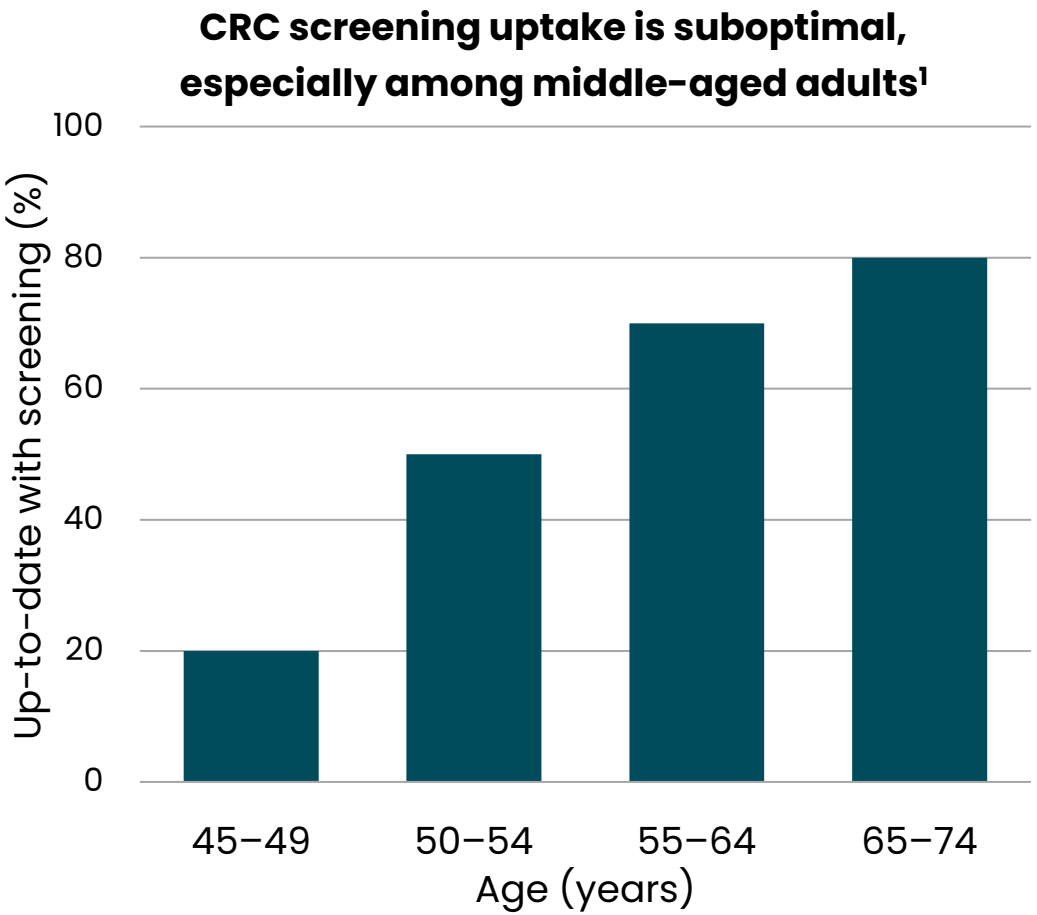
Background and Aims

CRC screening saves lives: New technologies may improve adherence



- CRC screening tests reduce mortality by[1]
  - Detection of cancer at earlier stages
  - Prevention by adenoma detection/removal
- Existing screening tests have limitations[2]
  - Colonoscopy is invasive and inconvenient
  - Patients reluctant to handle stool samples
- Emerging blood-based tests, which promise to improve uptake and adherence,[3] have
  - Higher sensitivity for CRC vs FIT[4]
  - Importantly, lower sensitivity for AA vs FIT[4,5]
- AGA panel suggested blood tests may expand screening but not replace current tests[6]

1. Siegel RL, et al. CA *Cancer J Clin*. 2023;73:233-54; 2. Meester RGS, et al. *Am J Gastroenterol*. March 20, 2024 [Online ahead of print]; 3. Coronado GD, et al. *Gut*. 2024;73:622-28; 4. Chung DC, et al. *N Engl J Med* 2024;390:973-83; 5. Piscitello AJ, et al. *J Med Screen*. 2023;30:175-83. 6. Lieberman D, et al. *Clin Gastroenterol Hepatol*. 2024:S1542-3565(24)00162-9

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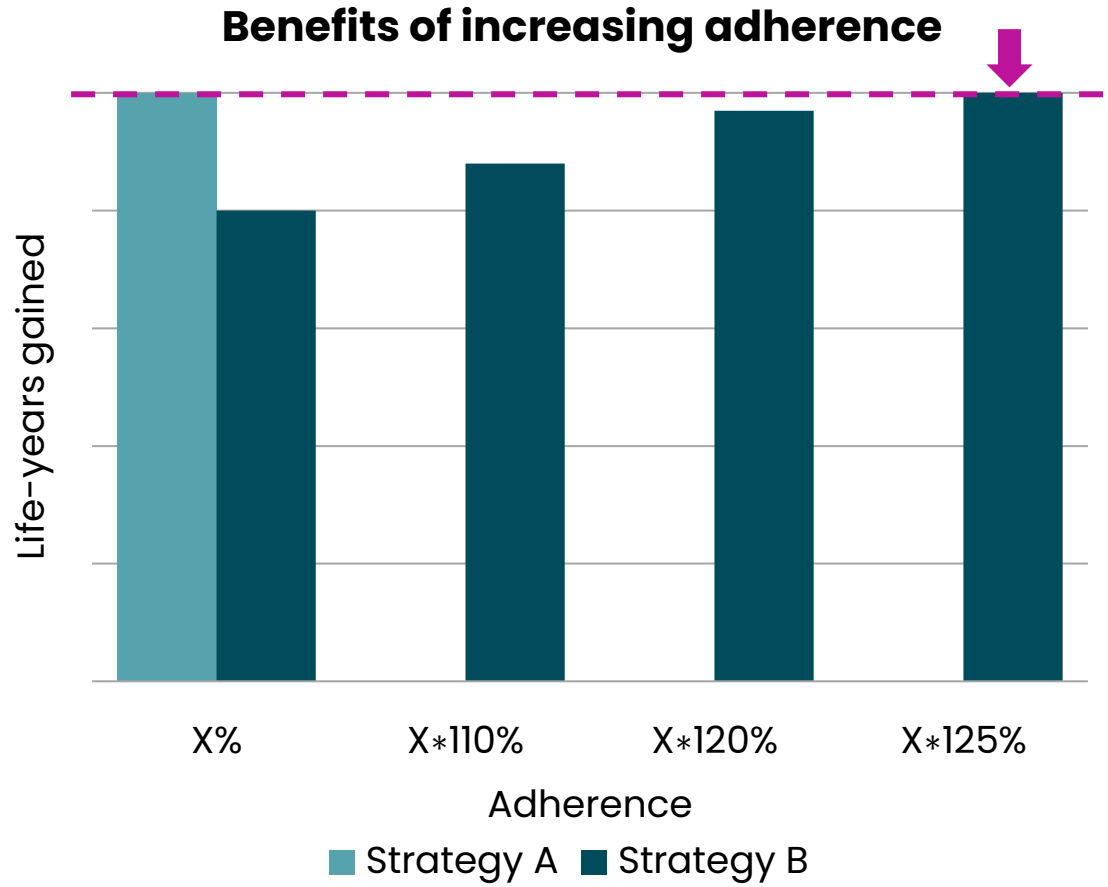
Study rationale: Increased adherence offsets lower test sensitivity

- Hypothesis: There's a "**critical adherence**" value at which blood-based screening offers benefits equivalent to stool-based screening, despite lower AA sensitivity
  - In this context, critical adherence is
    - The additional adherence, relative to stool-based screening, required to achieve equal LYG
    - The tipping point at which increased adherence vs. stool-based tests would offset potential increased mortality due to fewer AAs detected



In this example, critical adherence is +25% for Strategy B vs. Strategy A

(X is the baseline fraction of individuals adherent to screening)

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Study objective: Modeling comparative CRC screening test benefits

- We created a microsimulation model to assess the impact of CRC screening tests—each with different performance characteristics—on a variety of patient outcomes

Our model identified critical adherence values at which blood-based tests produce similar benefits to stool-based tests

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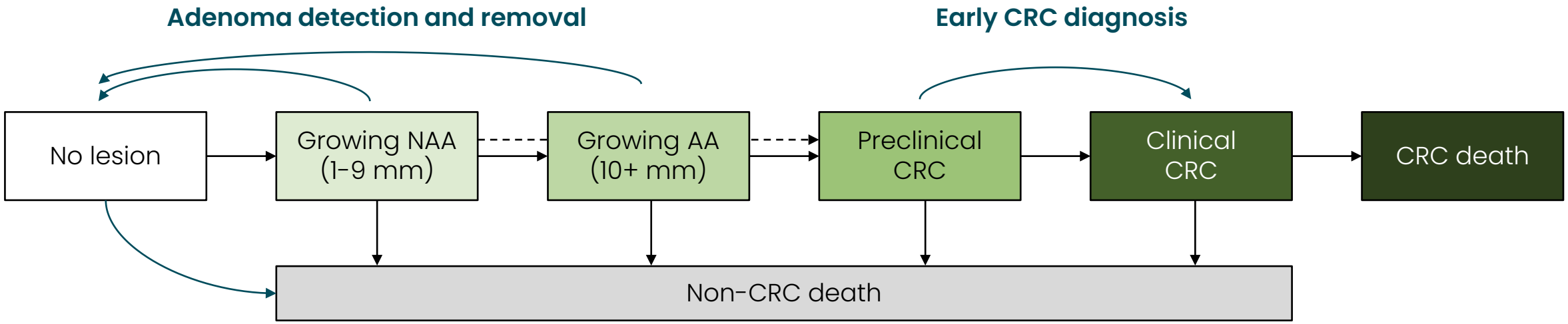
Methods

Microsimulation modeling of blood-based vs stool-based screening

- A well-documented Cancer Intervention and Surveillance Modeling Network model (called CRC-SPIN)[1] was replicated, to compare screening from age 45 to 75 y using different tests
  - Varied AA sensitivity for hypothetical blood-based CRC tests
  - Examined impact of adherence to blood-based tests at different levels of AA sensitivity
  - Estimated potential long-term benefits in terms of LYG per 1000 adults screened



NAA, non-advanced adenoma.

Figure adapted from Knudsen AB, et al. *JAMA*. 2021;325:1998-2011. 1. National Cancer Institute, Cancer Intervention and Surveillance Modeling Network. Colorectal Cancer Model Profiles. https://cisnet.cancer.gov/colorectal/profiles.html. Accessed March 21, 2024.

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Model assumptions testing two hypothetical blood-based tests

Assumptions	Colonoscopy[1]	FIT[1]	sDNA-FIT[1]	minBT	maxBT
Specificity for no lesions	86%	97%	91%	90%	90%
Sensitivity for NAA	75-85%	7%	15%	10%	10%
Sensitivity AA	95%	22%	42%	10%	50%
Sensitivity for CRC	95%	74%	94%	74%	74%
Test interval	-	1 y	1 or 3 y	1 or 3 y	1 or 3 y
Adherence	100%	Varied	Varied	Varied	Varied

Different AA sensitivity & adherence levels were evaluated in critical adherence analyses

Two hypothetical CRC blood-based tests, minBT and maxBT, were compared to existing tests
- For both, we assumed 74% CRC sensitivity and 90% specificity per minimum U.S. criteria[2]
- minBT and maxBT differ only by AA sensitivity (10% vs 50%)

1. Knudsen AB, et al. *JAMA*. 2021;325:1998-2011; 2. Centers for Medicare & Medicaid Services. National Coverage Analysis: Screening for Colorectal Cancer - Blood-Based Biomarker Tests. January 19, 2021. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=299. Accessed March 21, 2024.

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Various outcomes were assessed using the model

- Number of screening tests required
- Number of colonoscopies for follow-up and surveillance
- Lifetime CRC cases
- Lifetime CRC deaths
- LYG vs no screening
- Critical adherence for blood-based vs. stool-based screening

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Results

Lifetime outcomes of blood-based vs stool-based screening

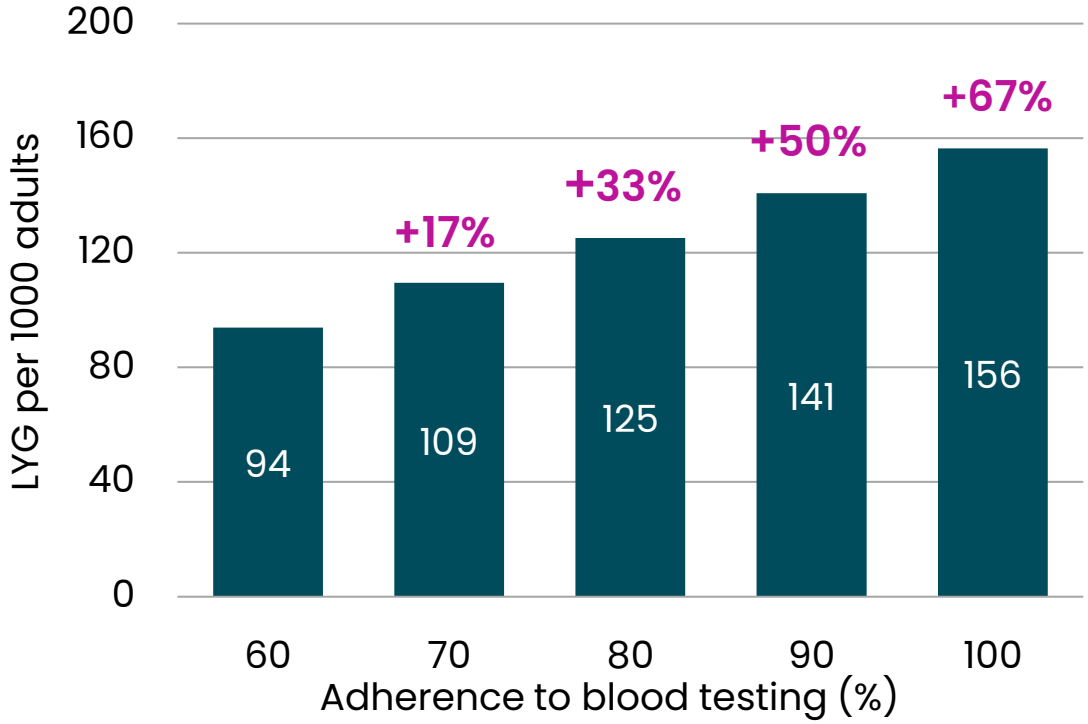
Outcomes per 1000 U.S. adults, with *hypothetical* 100% adherence rate

Strategies	Screening tests	Diagnostic & surveillance colonoscopies	CRC cases	% cases averted	CRC deaths	% deaths averted	LYG
No screening	-	71	70.7	-	27.1	-	-
minBT, 3 y	7,620	1,253	40.9	-42%	13.6	-50%	156.4
maxBT, 3 y	7,389	1,454	24.5	-65%	8.2	-70%	221.3
sDNA-FIT, 3 y	7,262	1,504	22.9	-68%	7.4	-73%	230.1
FIT, 1 y	18,974	1,549	19.6	-72%	6.0	-78%	247.7

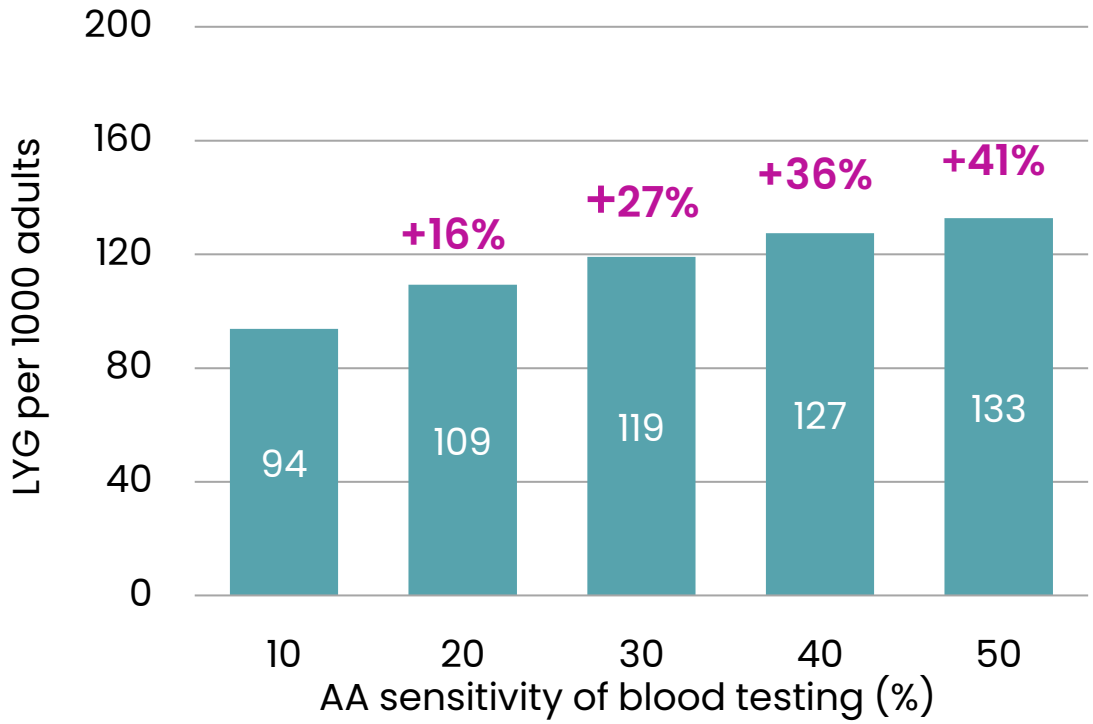
- Among 1000 unscreened adults, there were an estimated 70.7 lifetime CRC cases and 27.1 CRC deaths
- At 100% adherence, FIT would be the most effective test, followed by sDNA-FIT, maxBT, and then minBT
- FIT required nearly 3× the number of tests vs. other strategies; in reality, adherence is not 100%

Increasing adherence may have greater impact on LYG than increasing AA sensitivity

Impact of increased screening adherence on LYG for minBT*



Impact of increasing AA sensitivity from 10% (minBT) to 50% (maxBT) on LYG*



For a test with 60% adherence and 10% AA sensitivity (minBT)

- Increasing adherence by 40 percentage points increased LYG by 67%
- Increasing sensitivity by 40 percentage points increase LYG by 41%

*The number of LYG is displayed inside each bar; percentage increase in LYG is displayed above each bar.

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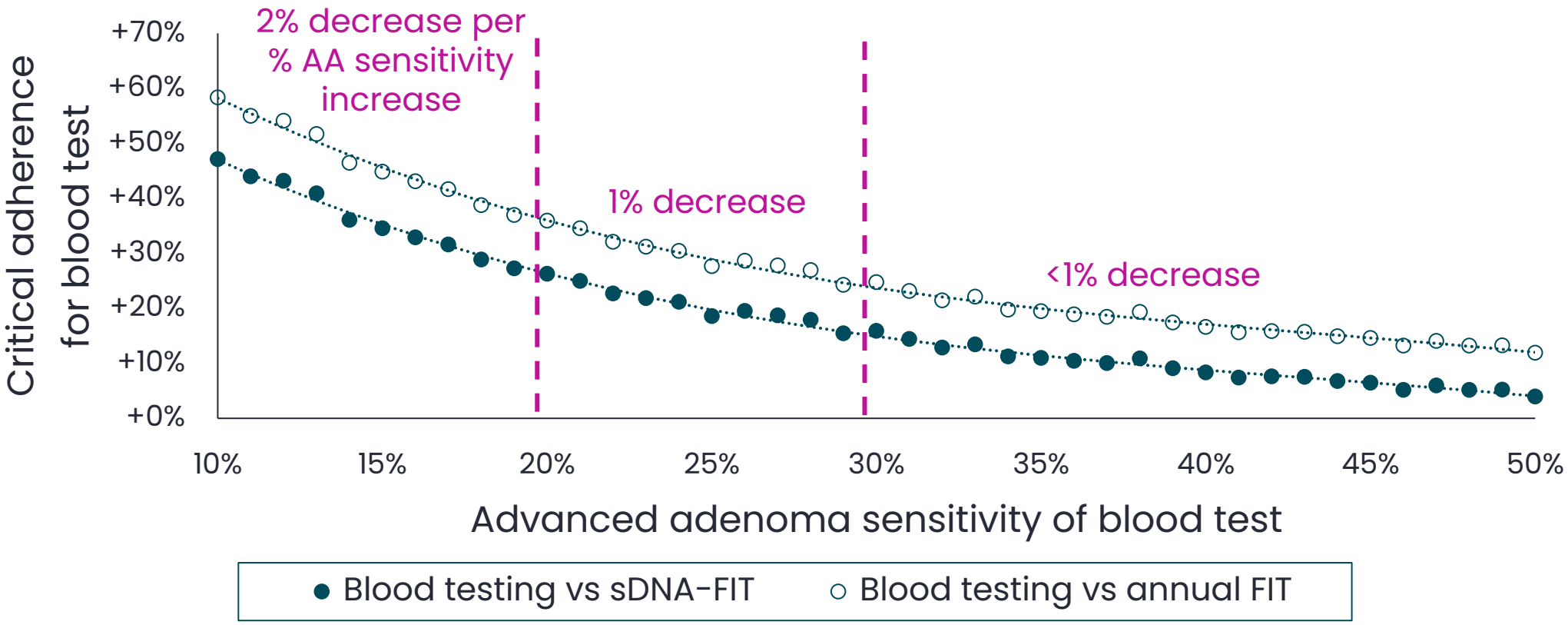
Critical adherence values—indicating similar benefit for tests being compared—decrease with increasing AA sensitivity



A blood test with moderate AA sensitivity of 20% would yield greater LYG when adherence is >26% higher vs sDNA-FIT and >36% higher vs FIT

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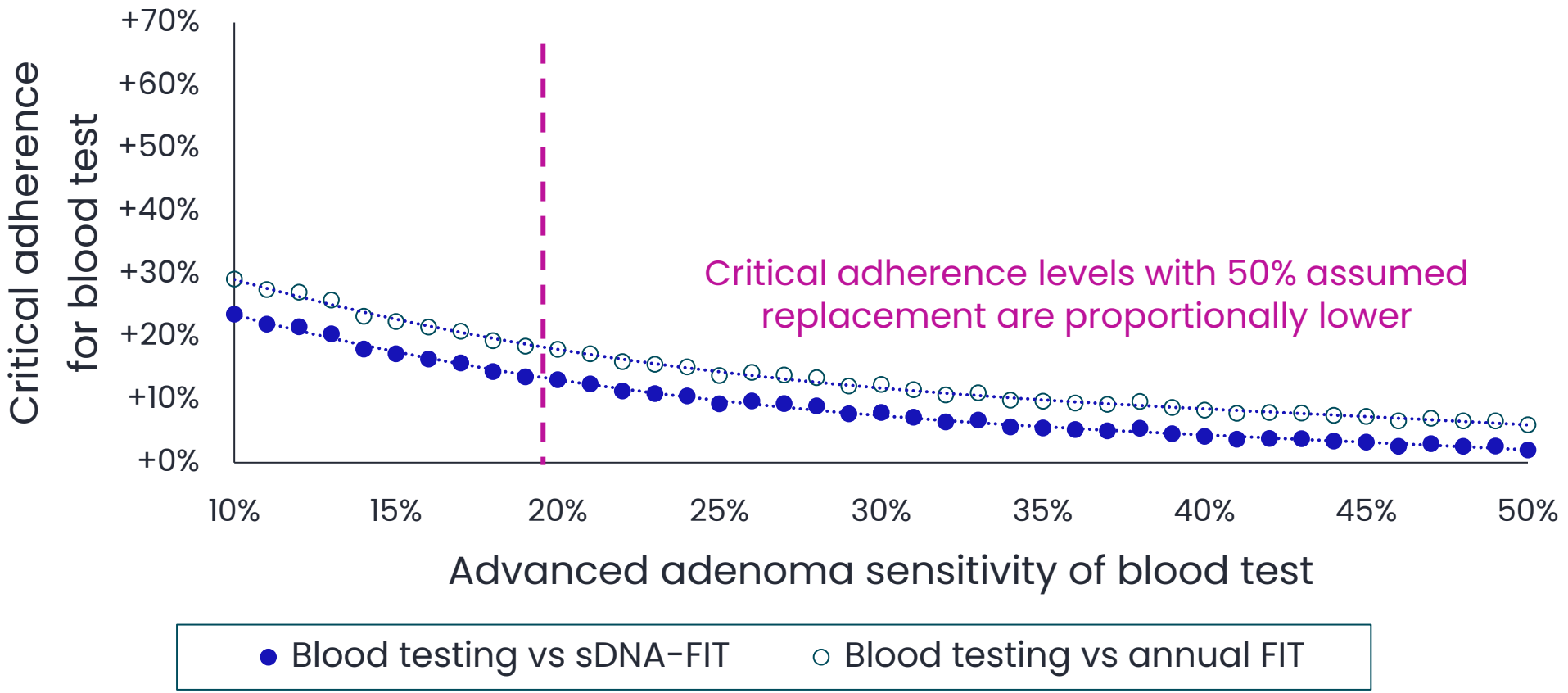
Critical adherence values decrease when assuming <100% replacement of stool testing



A blood test with moderate AA sensitivity of 20%, replacing half of stool-based testing, would yield greater LYG when adherence is >13% higher vs sDNA-FIT and >18% higher vs FIT

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Conclusions: Higher adherence can compensate for the potential lower AA sensitivity of blood-based CRC tests

- Adherence potentially has a greater impact on the benefit of blood-based vs stool-based screening than does AA sensitivity
- Novel, noninvasive CRC blood tests have the potential to improve CRC screening outcomes, especially when patients prefer that modality over existing tests
- Limitations
  - Annual blood-based screening was not shown but outcomes are more similar to FIT
  - NAA sensitivity and consistency of adherence are uncertain

"The best test is the one that gets done, and done well"

— Dr. Sidney J. Winawer [1]

1. Zauber AG. *Dig Dis Sci*. 2015;60:681-91.

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