WEO
The voice of world endoscopy

FIT positive: straight to colonoscopy or a second test to increase specificity?

Uri Ladabaum, M.D., M.S.
Professor of Medicine; Director, GI Cancer Prevention Program
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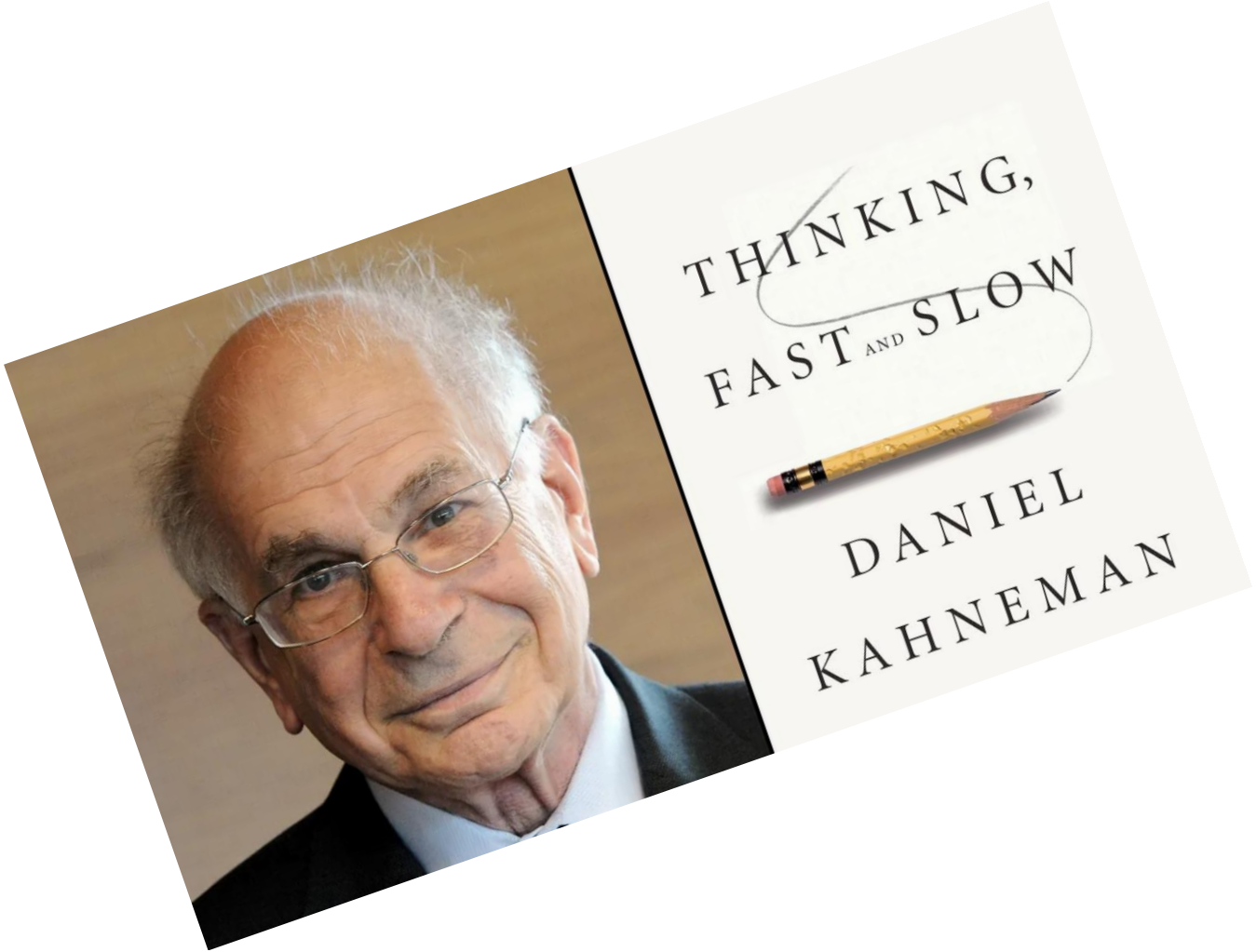
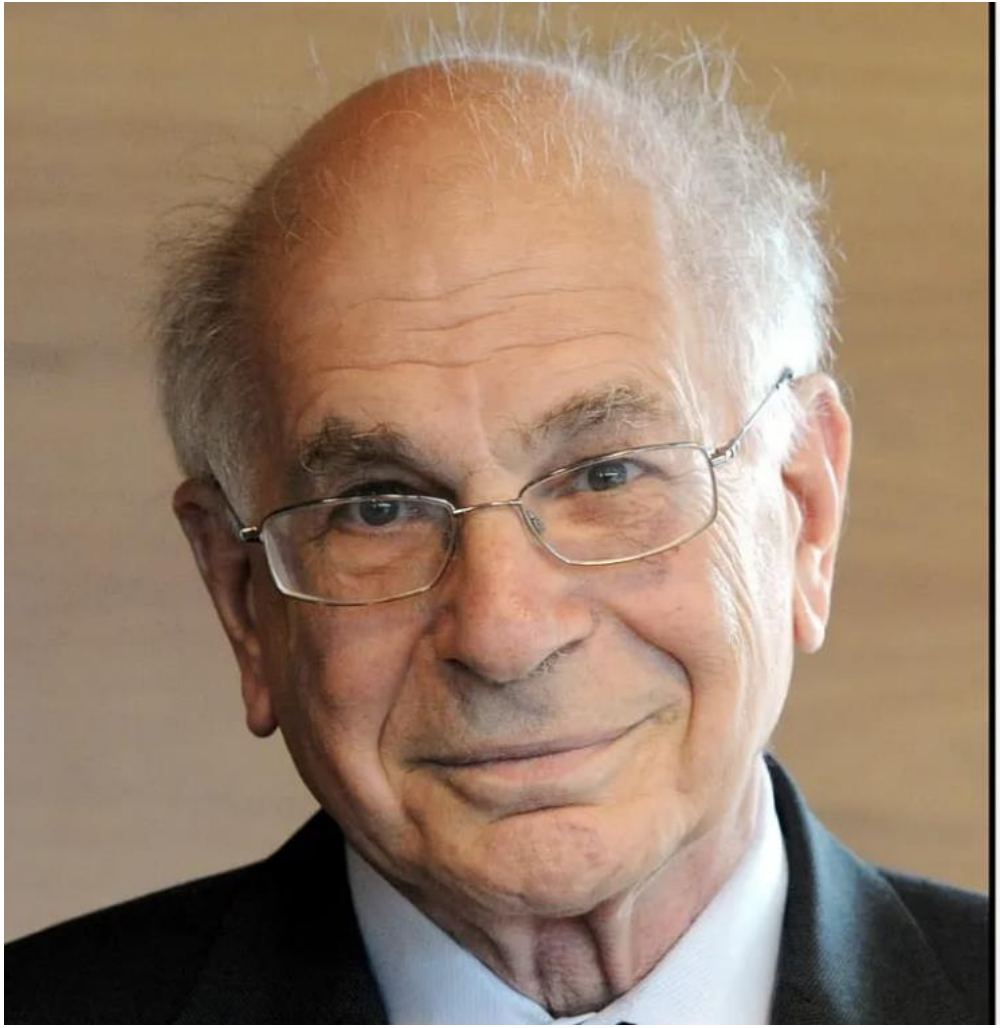
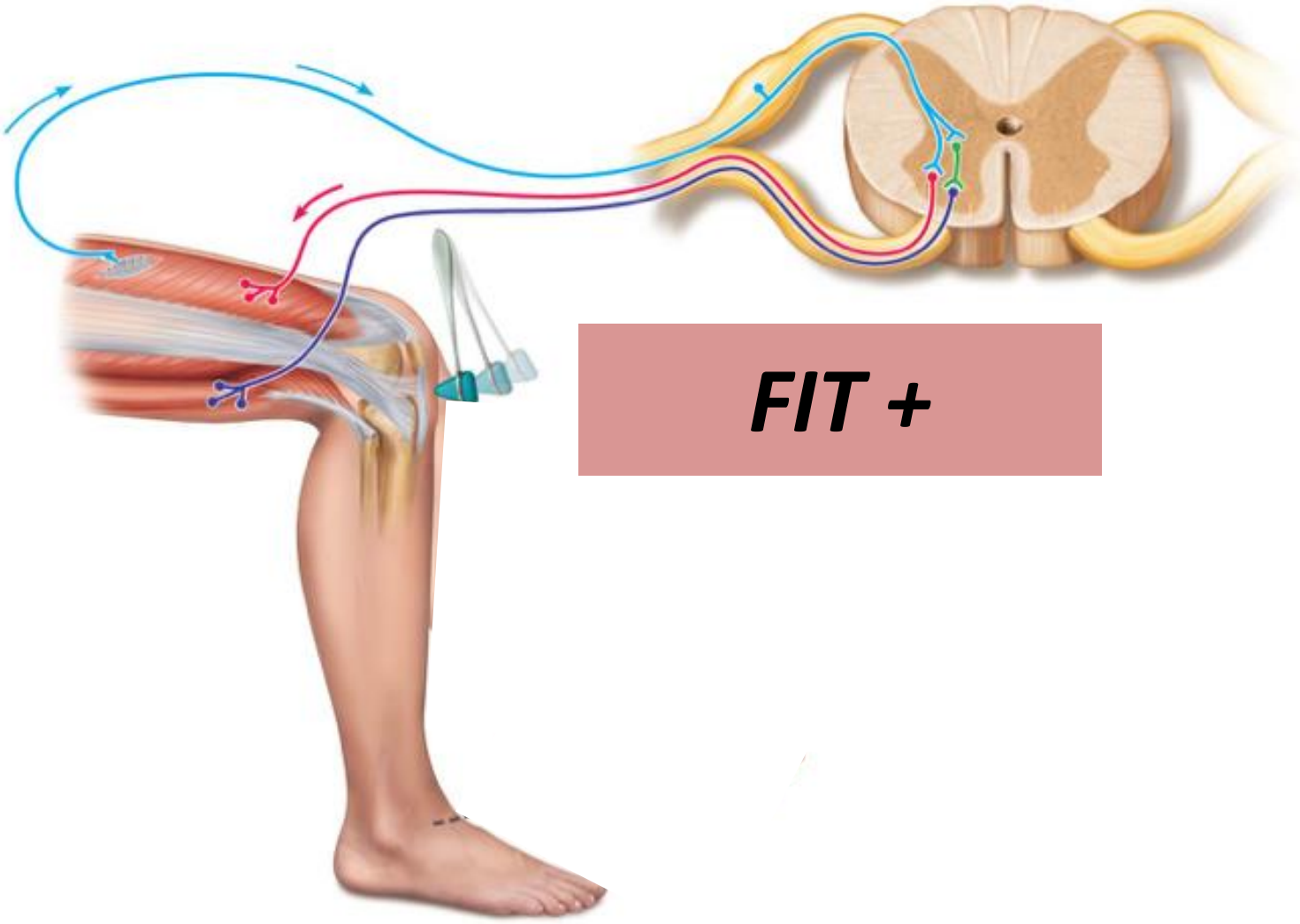

THINKING,
FAST AND SLOW
DANIEL
KAHNEMAN

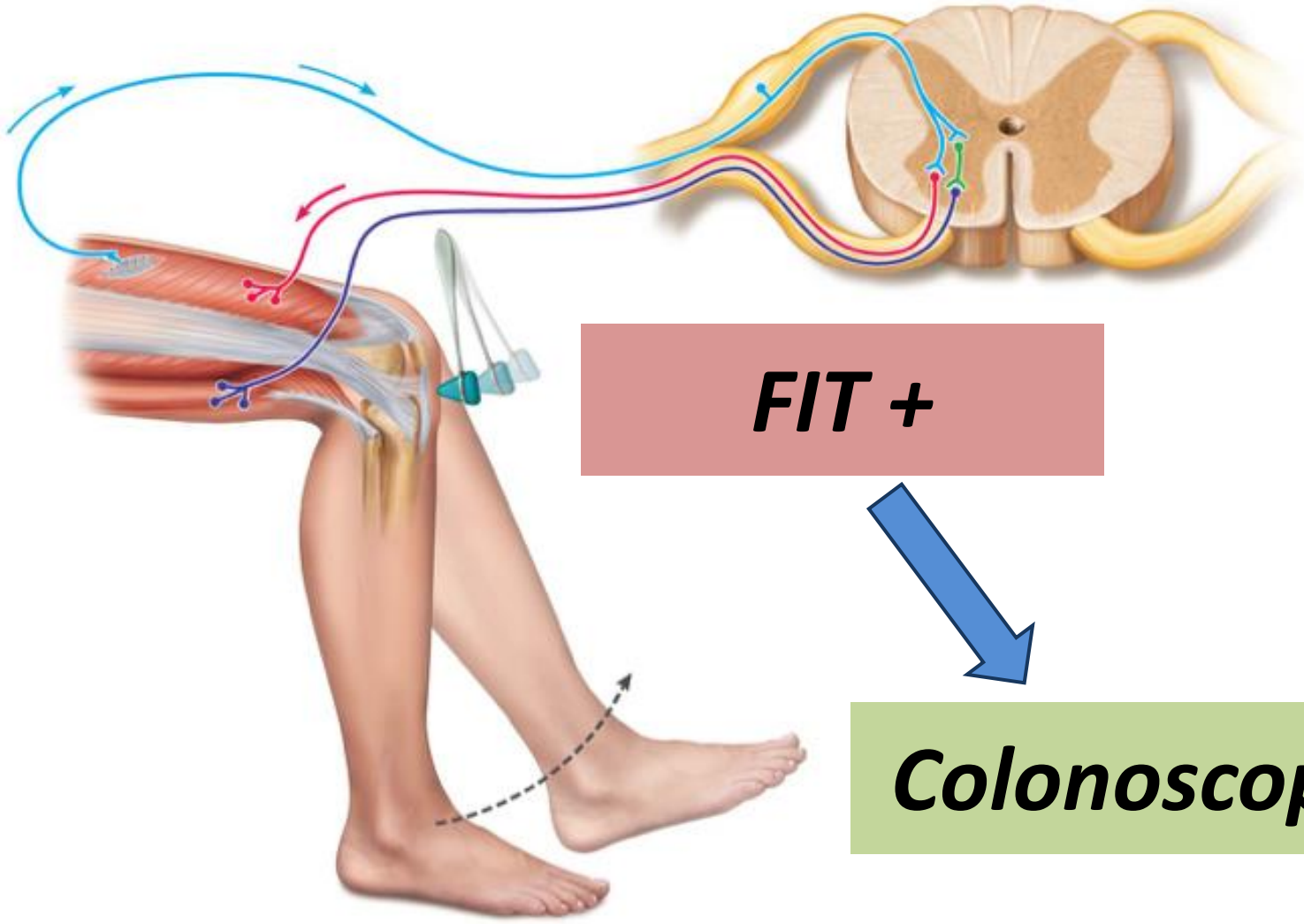


THINKING, FAST AND SLOW

DANIEL KAHNEMAN



FIT +



FIT +

Colonoscopy!

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The idea behind this topic

- Yield and positive predictive value (PPV) of FIT decrease over rounds
- Health authorities are critical of current yield at colonoscopy after FIT+

Agenda

- Why my initial reflex reaction?
- What would be required of the second (triage) test before colonoscopy?
- Possible future steps

Agenda

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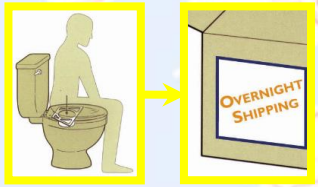
All roads lead to….

All roads lead to….

Colonoscopy


OVERNIGHT
SHIPPING


START!


START!


START!
OVERNIGHT
SHIPPING


START!


START!

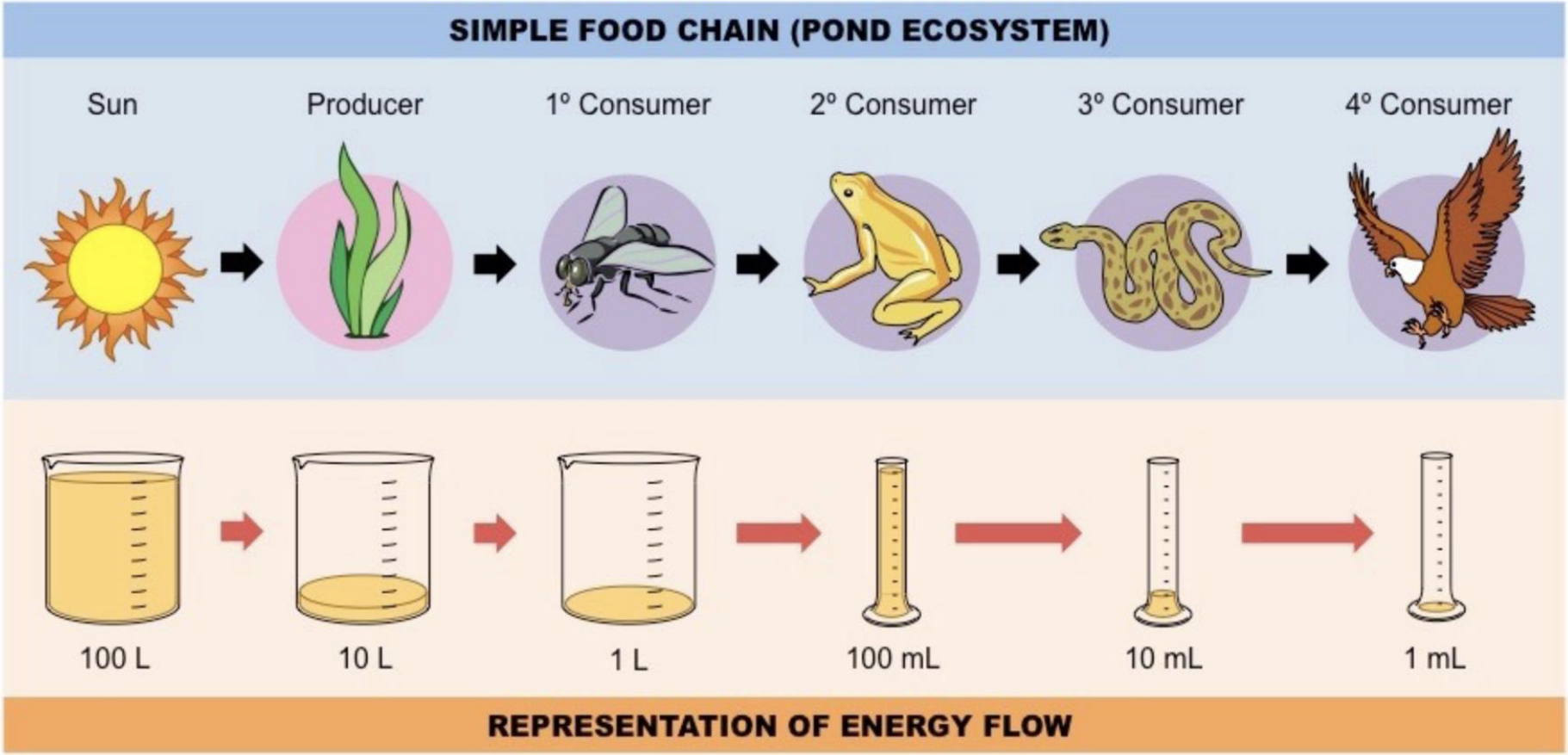

START!


START!
OVERNIGHT
SHIPPING

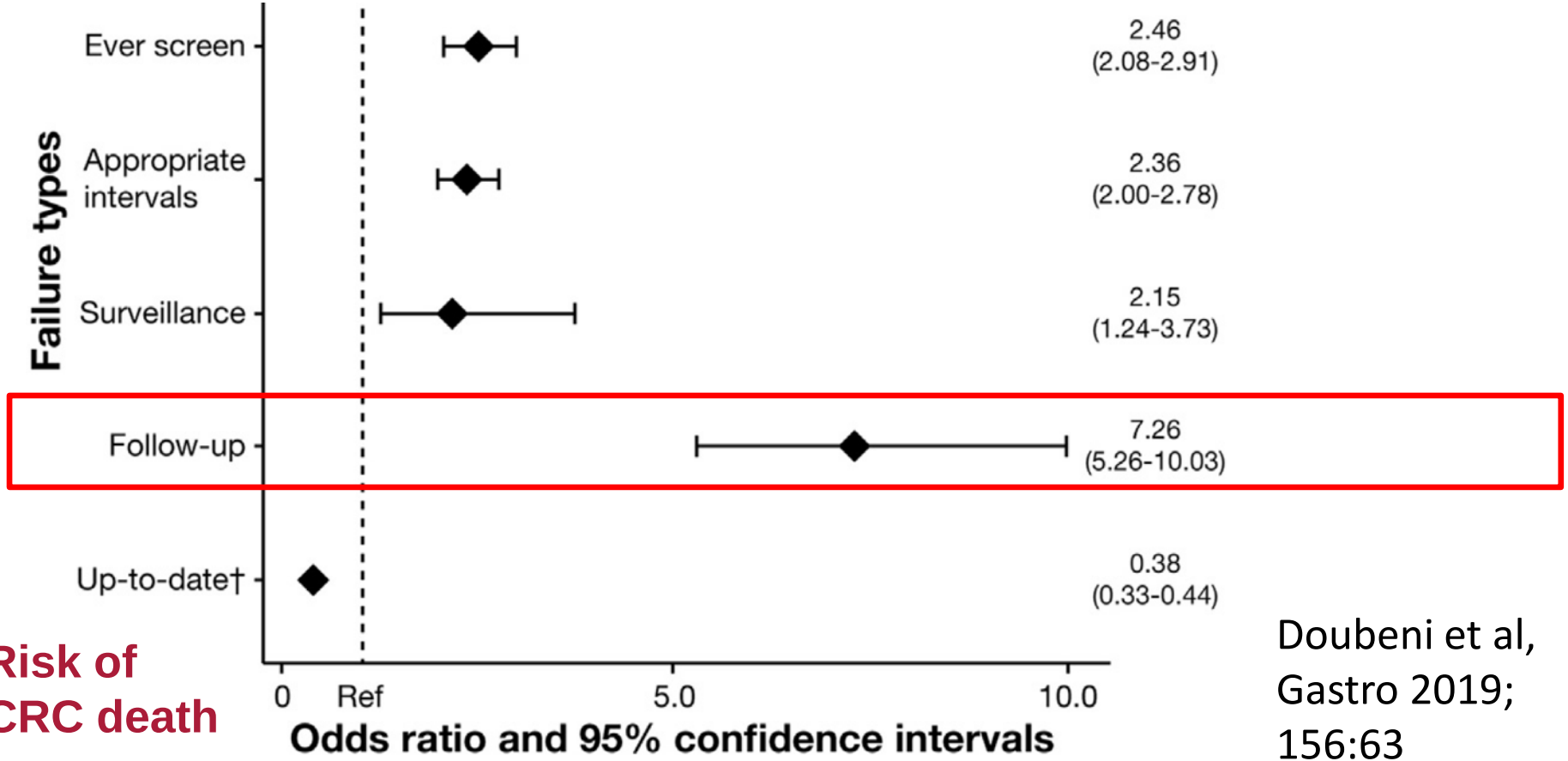

LANE 5
LANE 4
AUTOMATIC / OBU
TOLL LANE
LANE 3
MANUAL /
SEMI AUTOMATIC
TOLL LANE
LANE 2
STOP
STOP
STOP


START!

More steps → lower efficiency (e.g. energy in food chain)



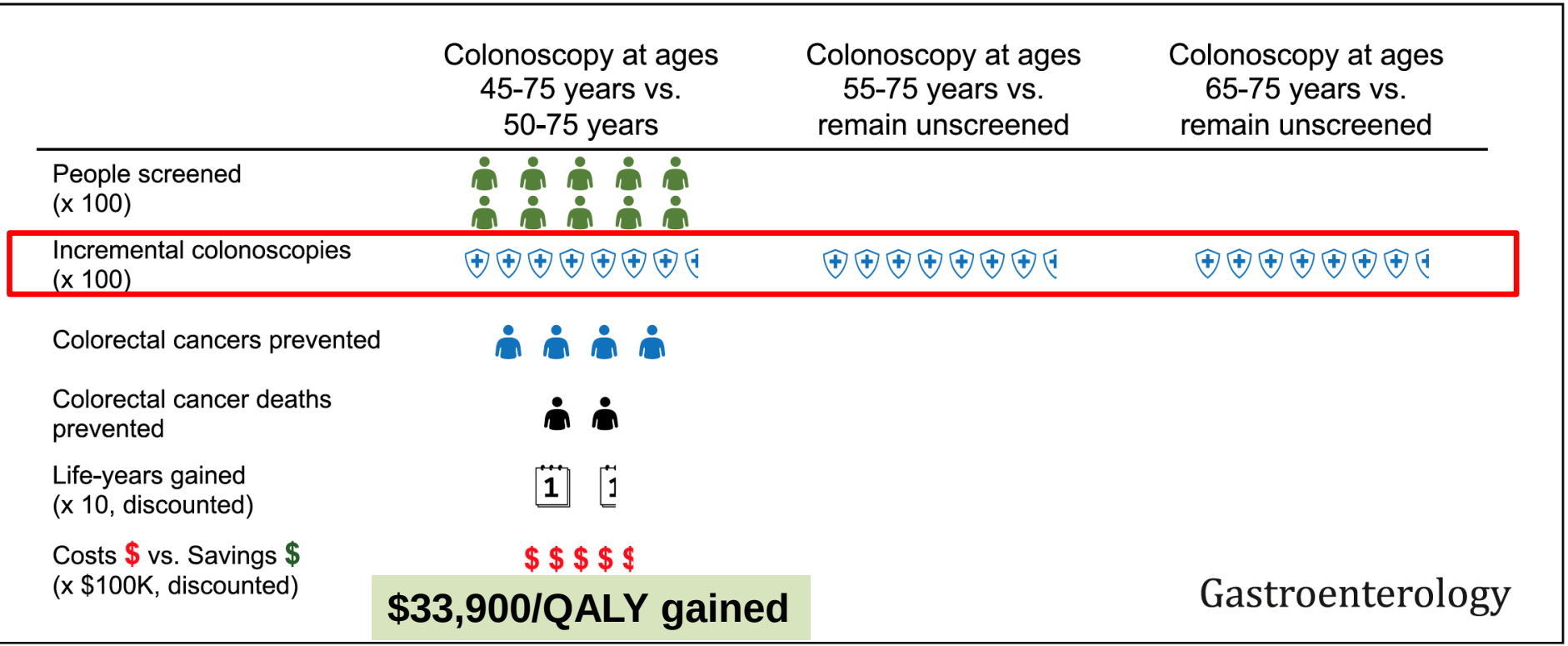
“Modifiable failures” in the *PROCESS*



Risk of CRC death

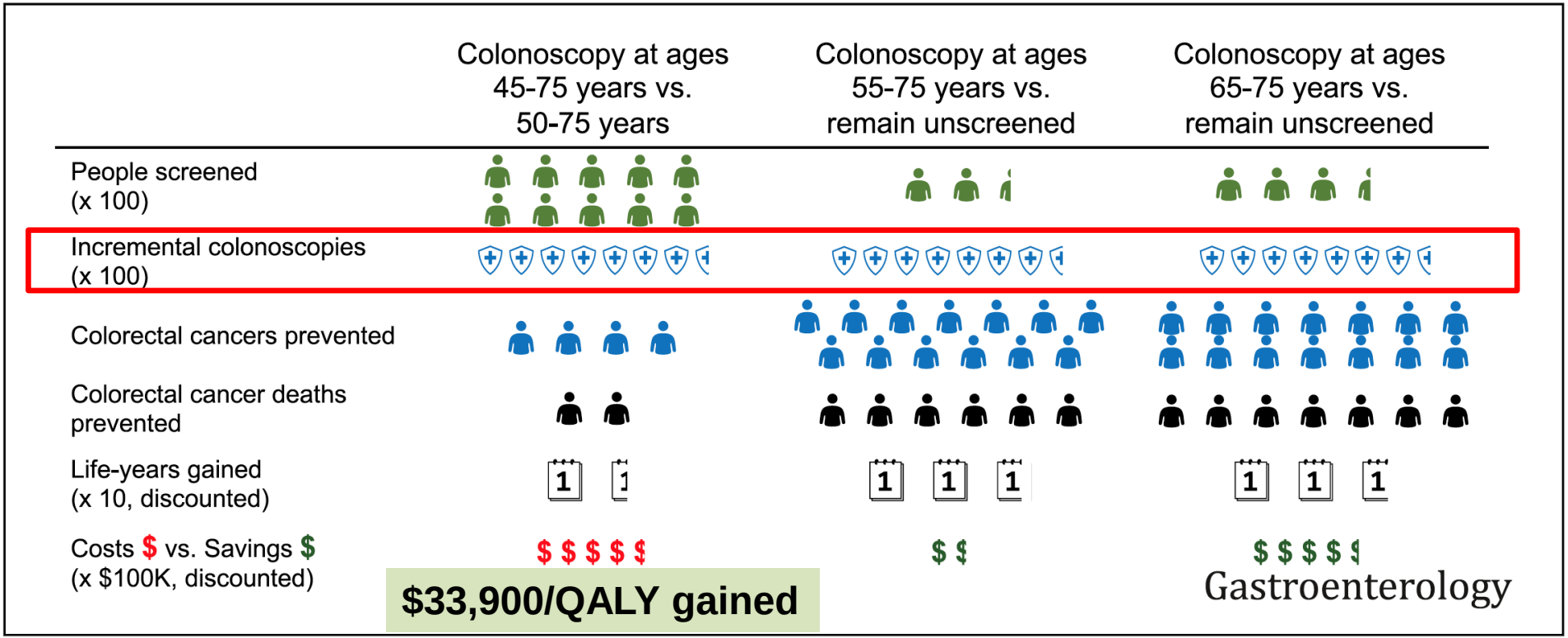
Doubeni et al, Gastro 2019; 156:63

Modeling effectiveness and cost-effectiveness



Ladabaum et al, Gastroenterology 2019;157:137

Modeling effectiveness and cost-effectiveness



Ladabaum et al, Gastroenterology 2019;157:137

Modeling effectiveness and cost-effectiveness

	Scenario 1: start screening colonoscopy every 10 years at age 45 instead of 50 years	Scenario 2: provide screening colonoscopy every 10 years to currently unscreened 55-year-olds	Scenario 3: provide screening colonoscopy every 10 years to currently unscreened 65-year-olds	Scenario 4: increase follow-up colonoscopy completion rate after abnormal FIT result from 60% to 90% in cohort currently participating in annual FIT[a]
Cohort size, n	1000	231	342	3935[b]
Incremental number of colonoscopies required over a lifetime, n	758	758	758	758
CRC cases averted, n	4	13	14	22
CRC deaths averted, n	2	6	7	10
Absolute gain in QALYs (discounted)	14	28	27	36
Absolute incremental cost (discounted)[c]	$486,500	($163,700)	($445,800)	($843,900)

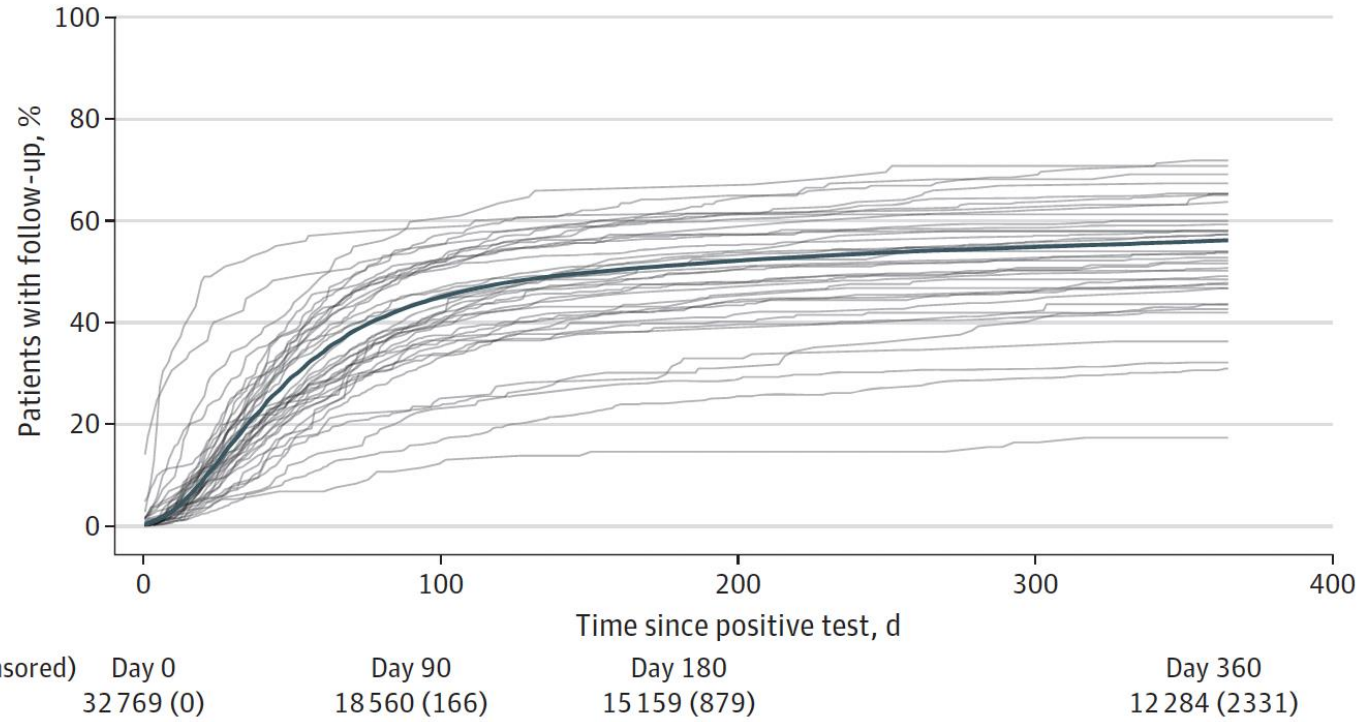
Ladabaum et al, Gastroenterology 2019;157:137

Poor StoolTest+ → Colonoscopy Rates

n=32,769
39 HCOs
2017-20

56.1%
overall f/u

Figure 2. Time-to-Event Curves for Follow-up Colonoscopy



Mohl et al, JAMA NetOp 2023;6:e2251384

Expanding quality metrics?

Gastroenterology 2022;163:520–526

AGA SECTION

Reducing the Burden of Colorectal Cancer: AGA Position Statements

David Lieberman,[1,*] **Uri Ladabaum**,[2,*] Joel V. Brill,[3,4] Folasade P. May,[5,6,7] Lawrence S. Kim,[8] Caitlin Murphy,[9] Richard Wender,[10] and Kathleen Teixeira[11]

Expanding quality metrics?

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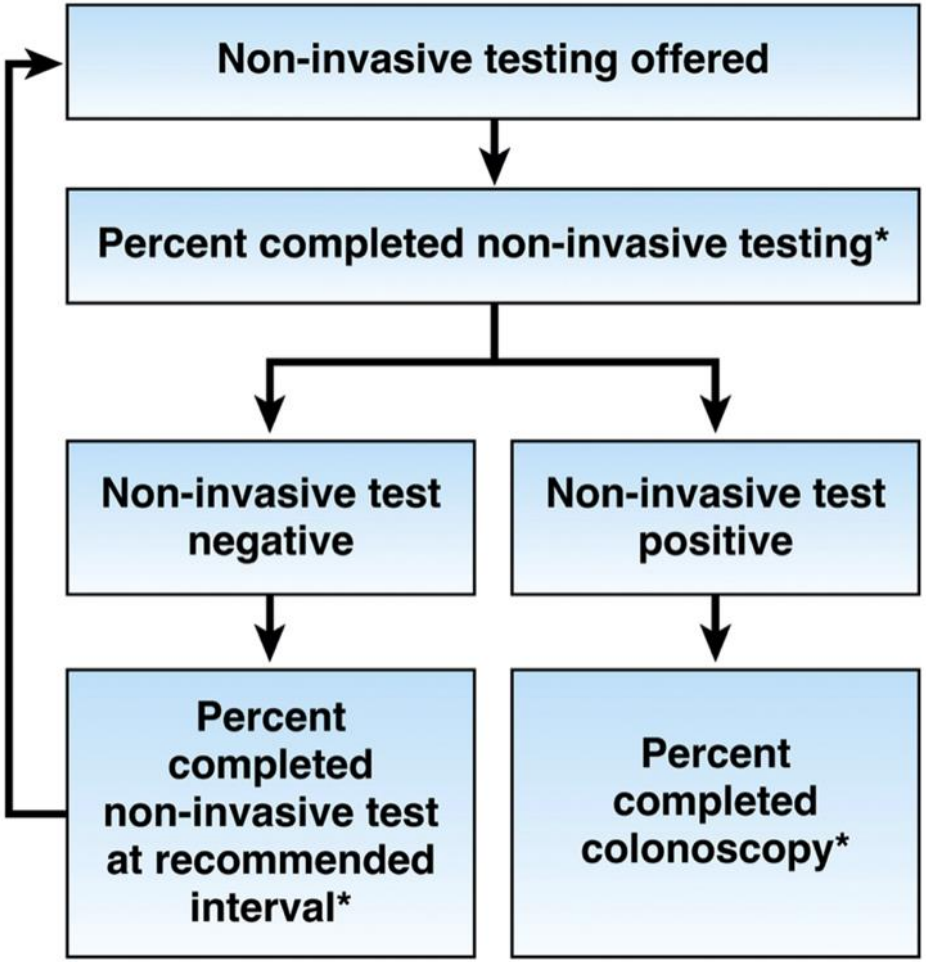

*Quality metrics for non-invasive screening program

Expanding quality metrics?

Gastroenterology 2022;163:520–526

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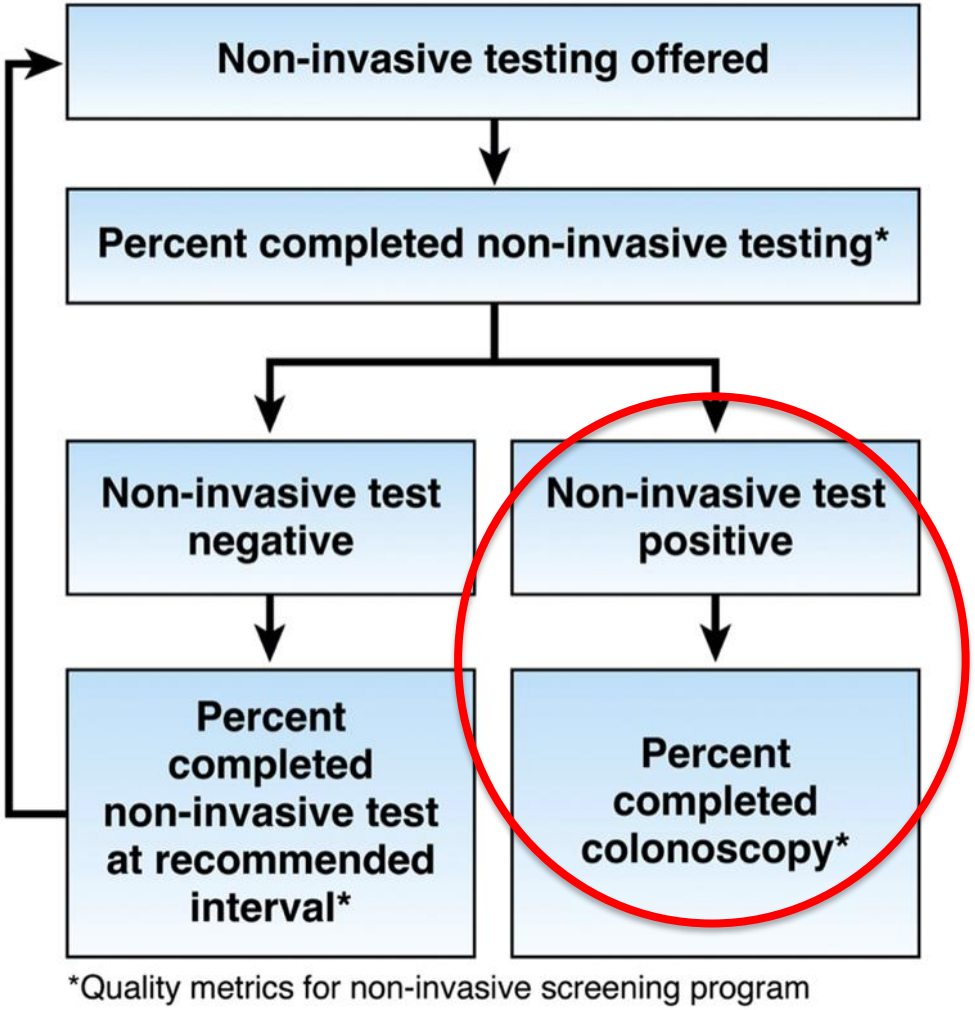

Sidney J. Winawer

"The best test is the one that gets done"

Winawer S, Dig Dis Sci 2015; 60:596-608

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

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Winawer S, Dig Dis Sci 2015; 60:596-608

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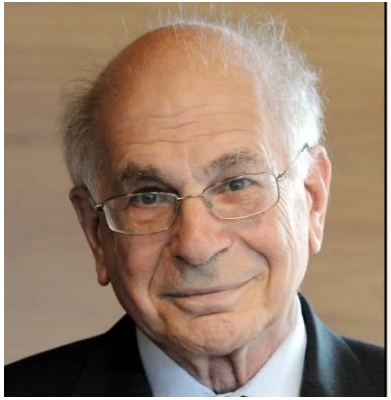

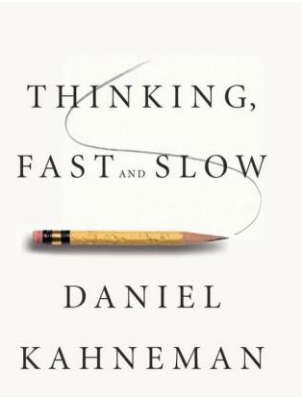

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Sidney J. Winawer

"Colorectal cancer screening is evidence-based but resource-driven"

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

Winawer S, Dig Dis Sci 2015; 60:596-608

“Colorectal cancer screening is evidence-based but resource-driven”

“The best test is the one that gets done and done well”

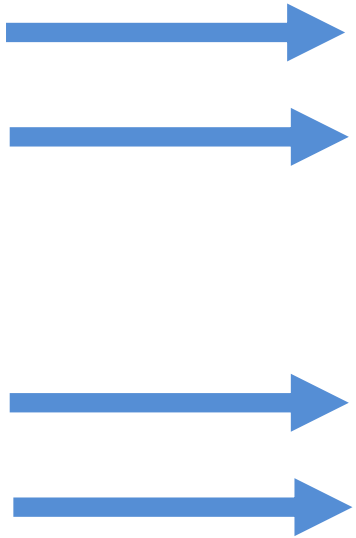
Participation

Quality

Sidney J. Winawer

“Colorectal cancer screening is evidence-based but resource-driven”

“The best test is the one that gets done and done well”



Science

Ethics

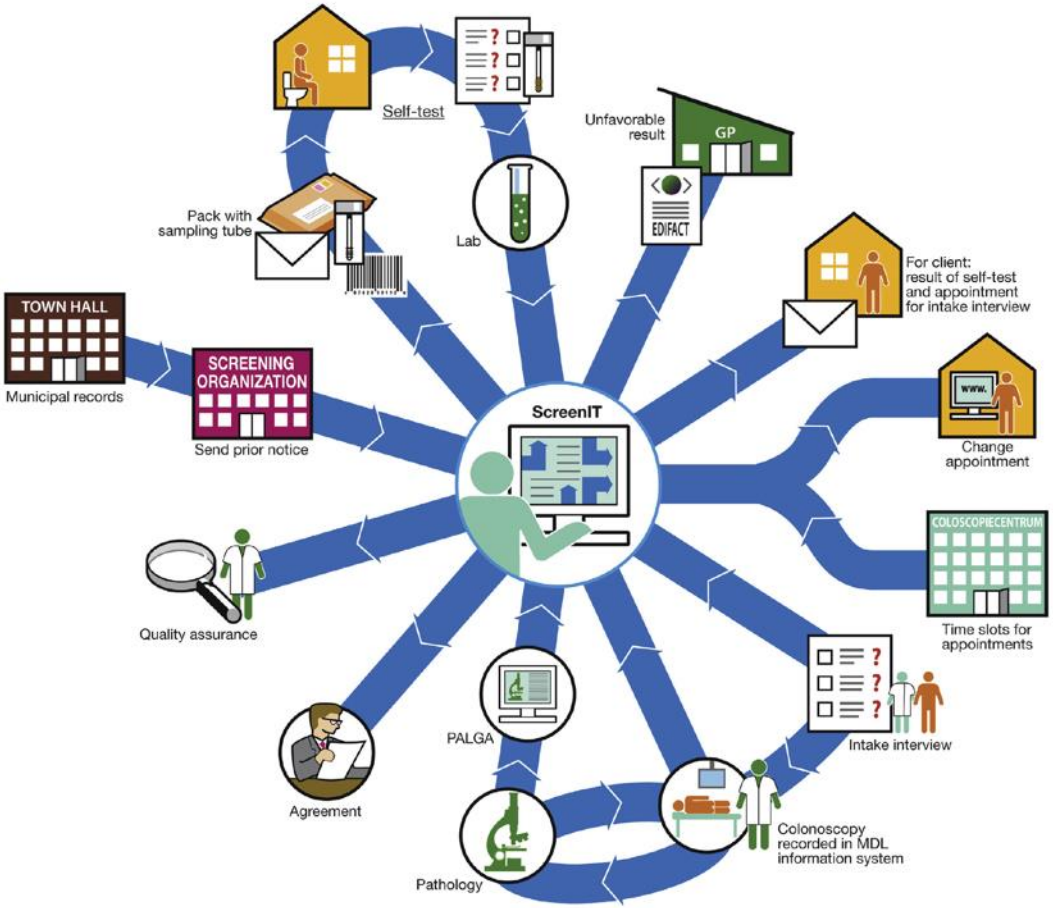
Economics

Participation

Quality

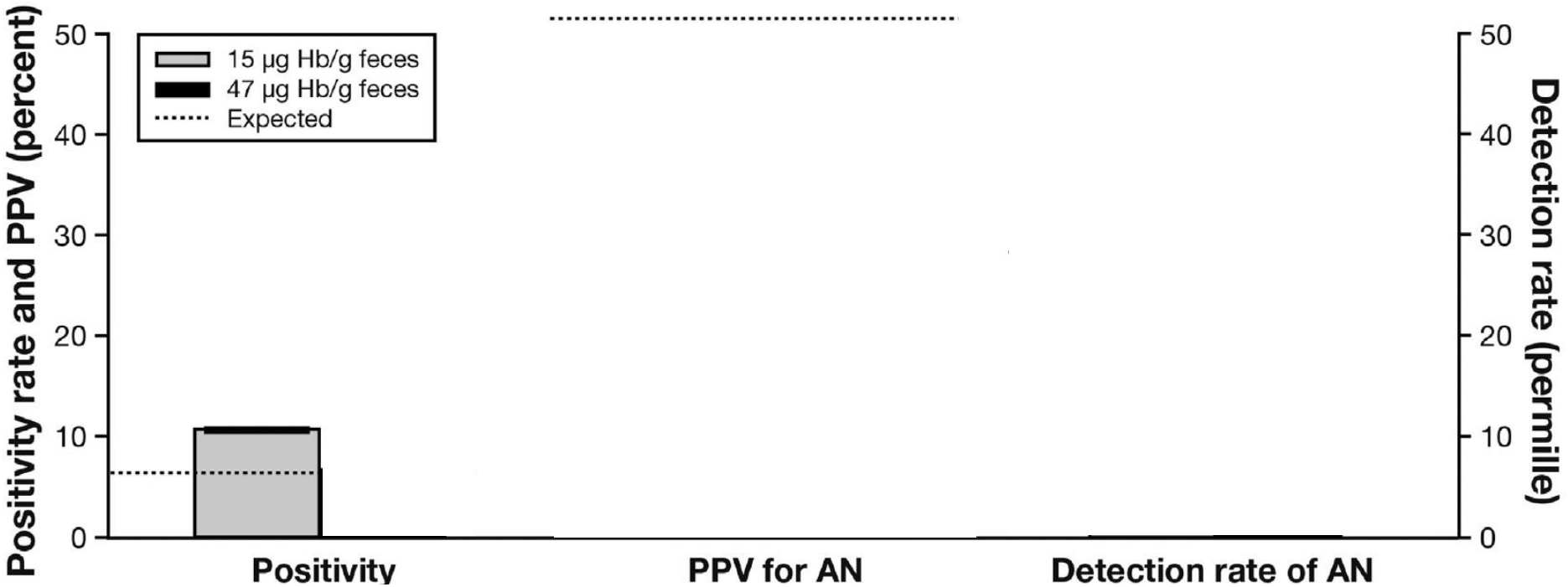
Sidney J. Winawer

Opportunistic vs. Organized: e.g. Dutch FIT program



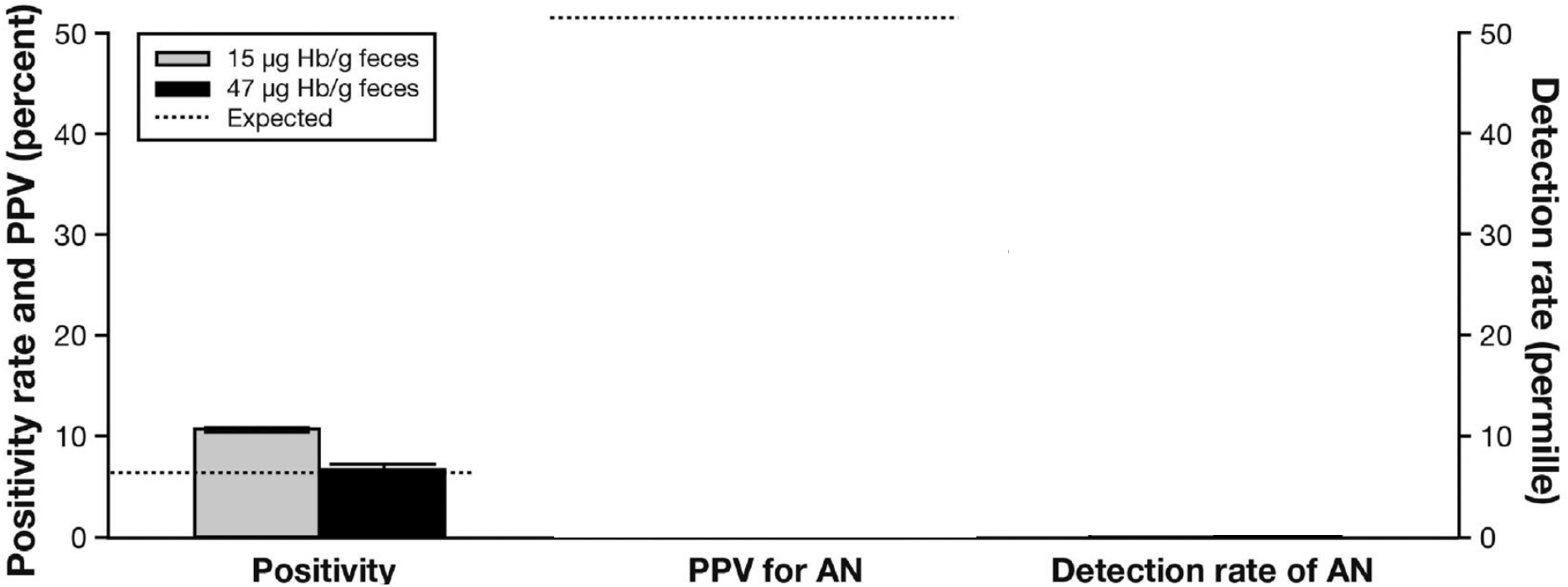
Toes-Zoutendijk et al,
Gastro 2017;152:767

2014: Higher participation/positivity/colo# than expected



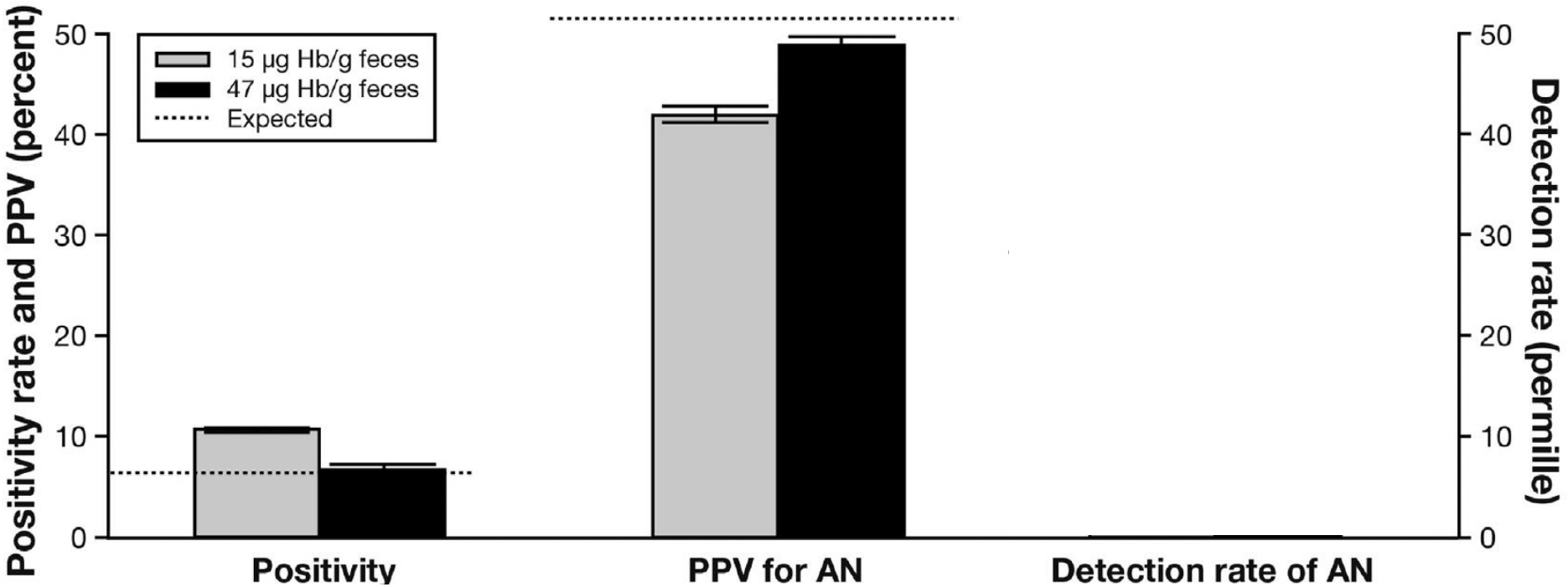
Toes-Zoutendijk et al, Gastro 2017;152:767

2014: Increase cut-off → lower positivity



Toes-Zoutendijk et al, Gastro 2017;152:767

2014: Increase cut-off → increase PPV / lower detection



Toes-Zoutendijk et al, Gastro 2017;152:767

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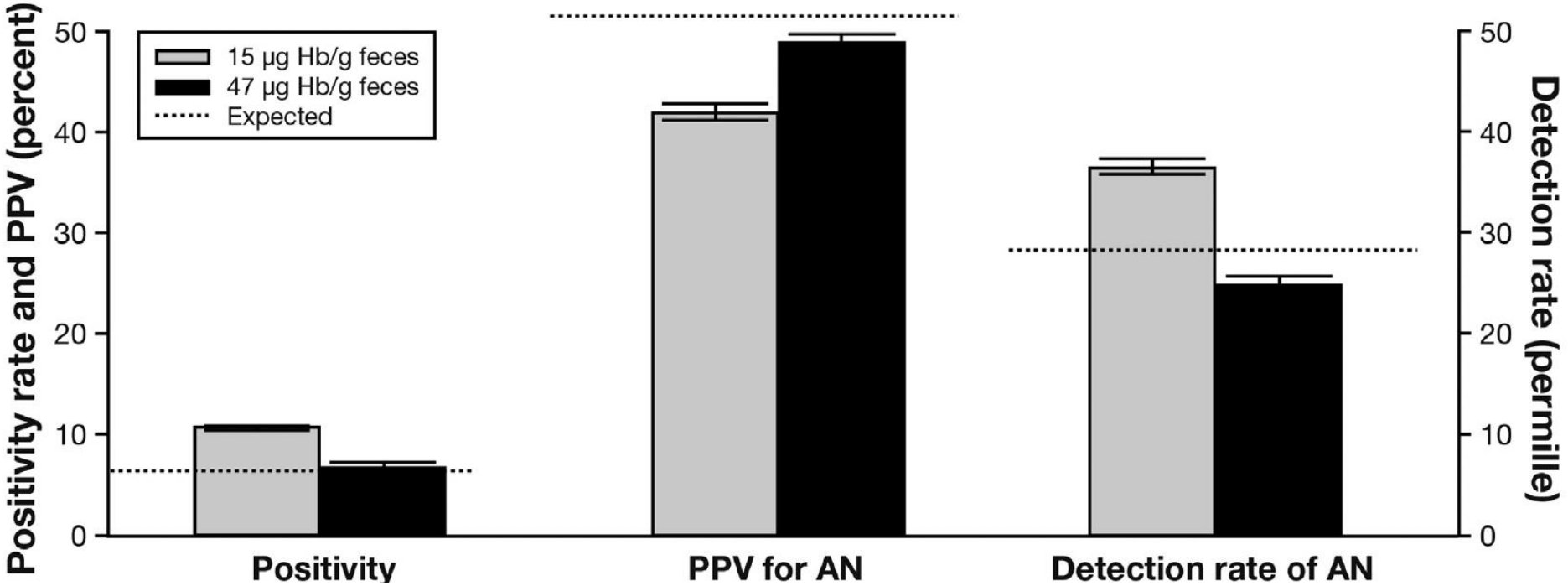

Toes-Zoutendijk et al, Gastro

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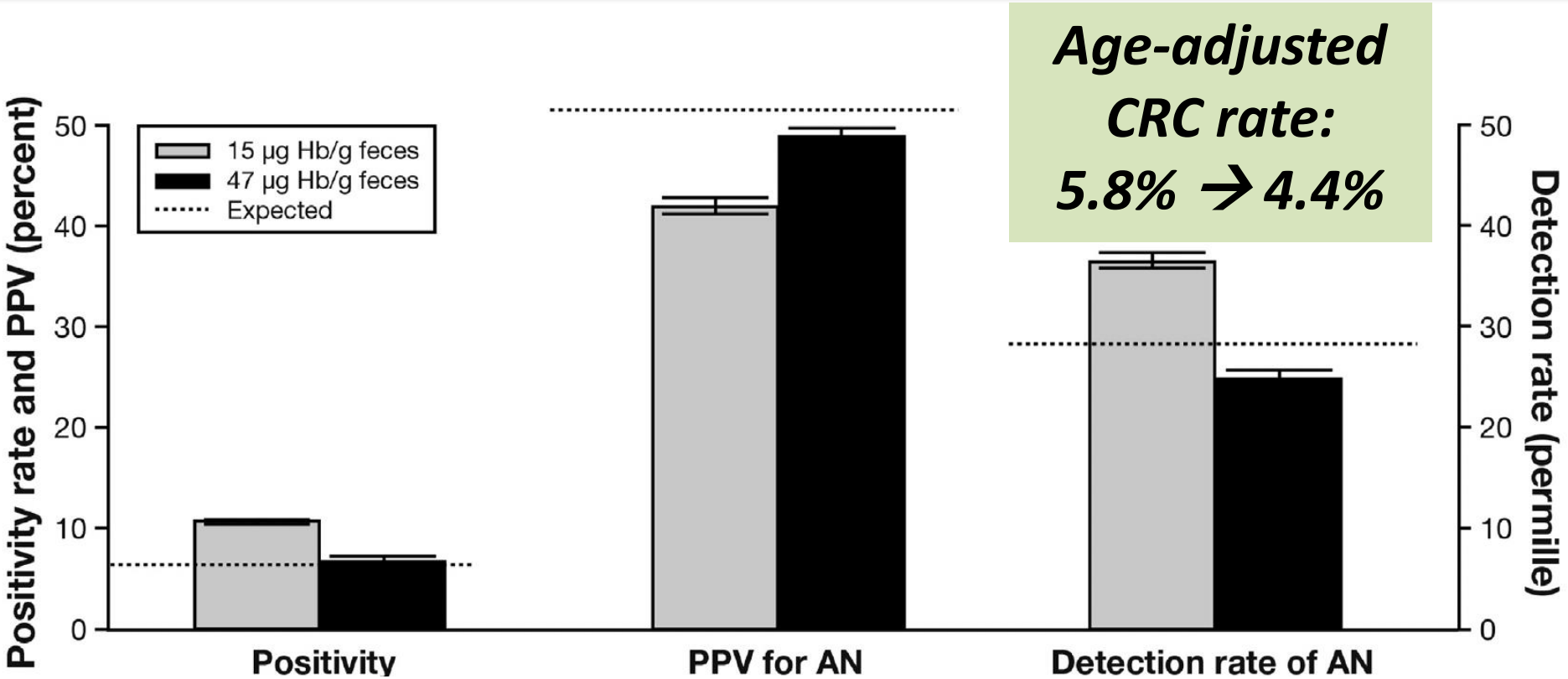

Toes-Zoutendijk et al, Gastro 2017;152:767

"Colorectal cancer screening is evidence-based but resource-driven"

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Sidney J. Winawer

FIT performance per round: Do we have a problem?

Round	1	2	3	4	5	6
Crude positivity	**5.7%**					
Crude PPV for advanced neoplasia	**36.9%**					
Number needed to scope to detect one case of advanced neoplasia	**2.7**					

Zorzi et al, Gut 2018;67:2124

FIT performance per round: Do we have a problem?

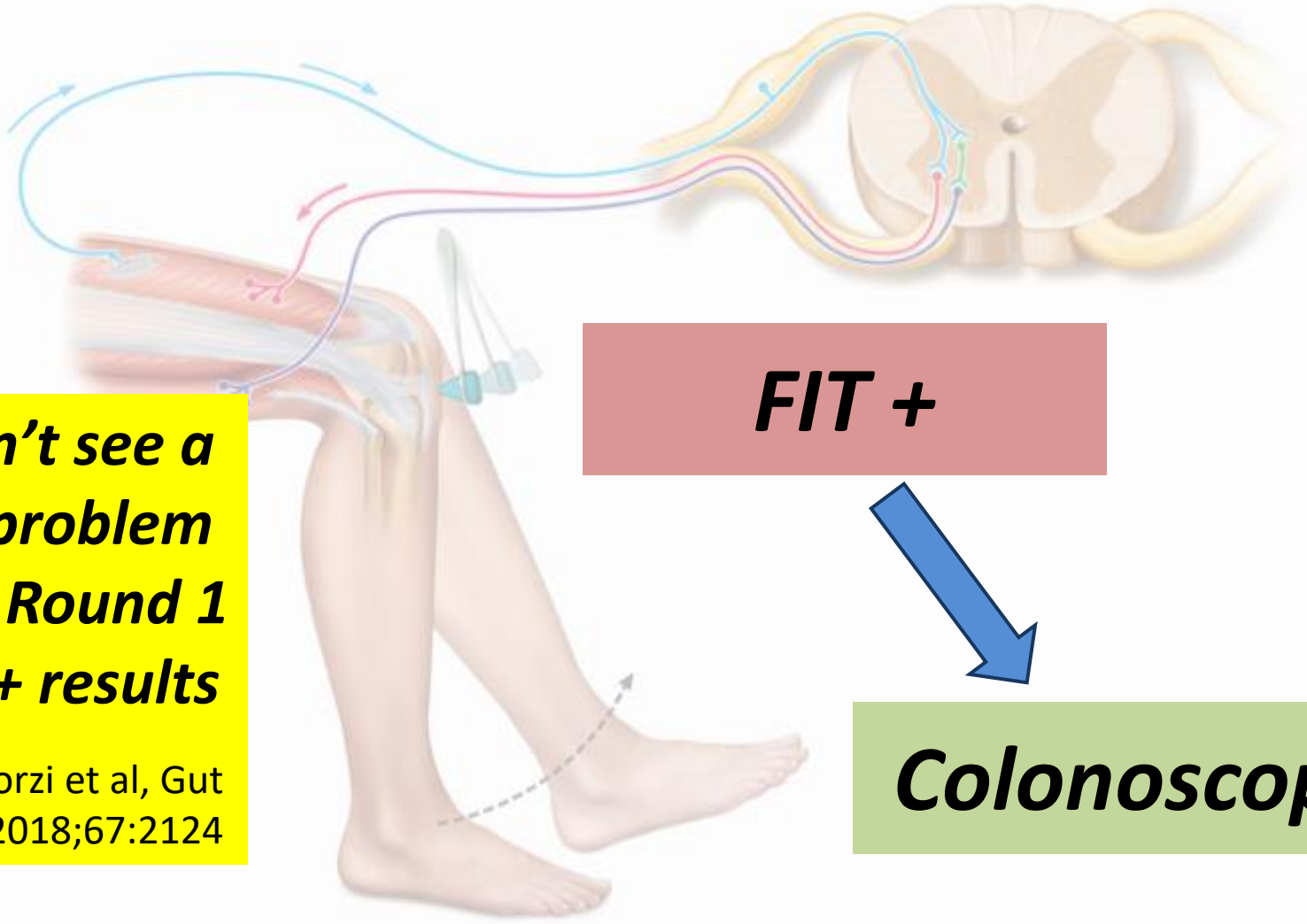
Round	1	2	3	4	5	6
Crude positivity	**5.7%**	3.6%				
Crude PPV for advanced neoplasia	**36.9%**	30.2%				
Number needed to scope to detect one case of advanced neoplasia	**2.7**	3.3				

Zorzi et al, Gut 2018;67:2124

FIT performance per round: Do we have a problem?

Round	1	2	3	4	5	6
Crude positivity	**5.7%**	3.6%	3.3%	3.3%	3.7%	3.8%
Crude PPV for advanced neoplasia	**36.9%**	30.2%	29.1%	30.0%	28.7%	30.2%
Number needed to scope to detect one case of advanced neoplasia	**2.7**	3.3	3.4	3.3	3.5	3.3

Zorzi et al, Gut 2018;67:2124



I don't see a big problem with Round 1 → 2+ results

Zorzi et al, Gut 2018;67:2124

FIT +

Colonoscopy!

A 3-step process?

(Really?)

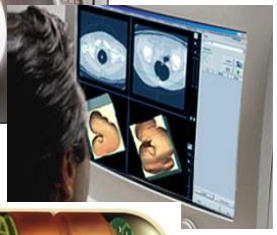
A 3-step process?

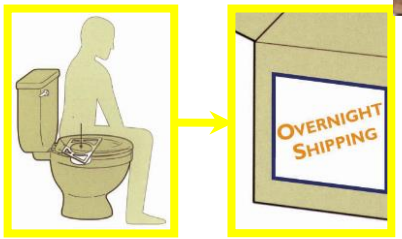
Step 1	Step 2	Step 3

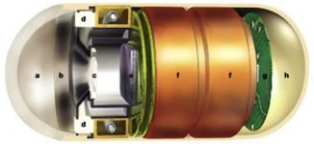
A 3-step process?

Step 1

Step 2



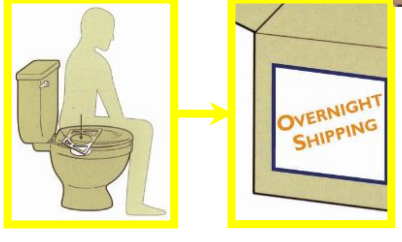




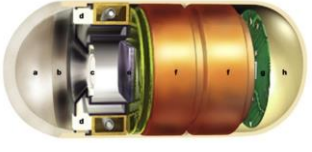
Step 3

A 3-step process?

Step 1



Step 2



Step 3

What do we need in Step 2?

Step 1 | **Step 2** | **Step 3**

- ***<u>Extremely</u> high sensitivity (can't lose persons with AN)…***
- ***High specificity (meant to "weed out" false-positive FIT)…***
- ***…in <u>FIT+ persons!</u>***
- ***[<u>May not be the same</u> as in the general screening-naïve population]***

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 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

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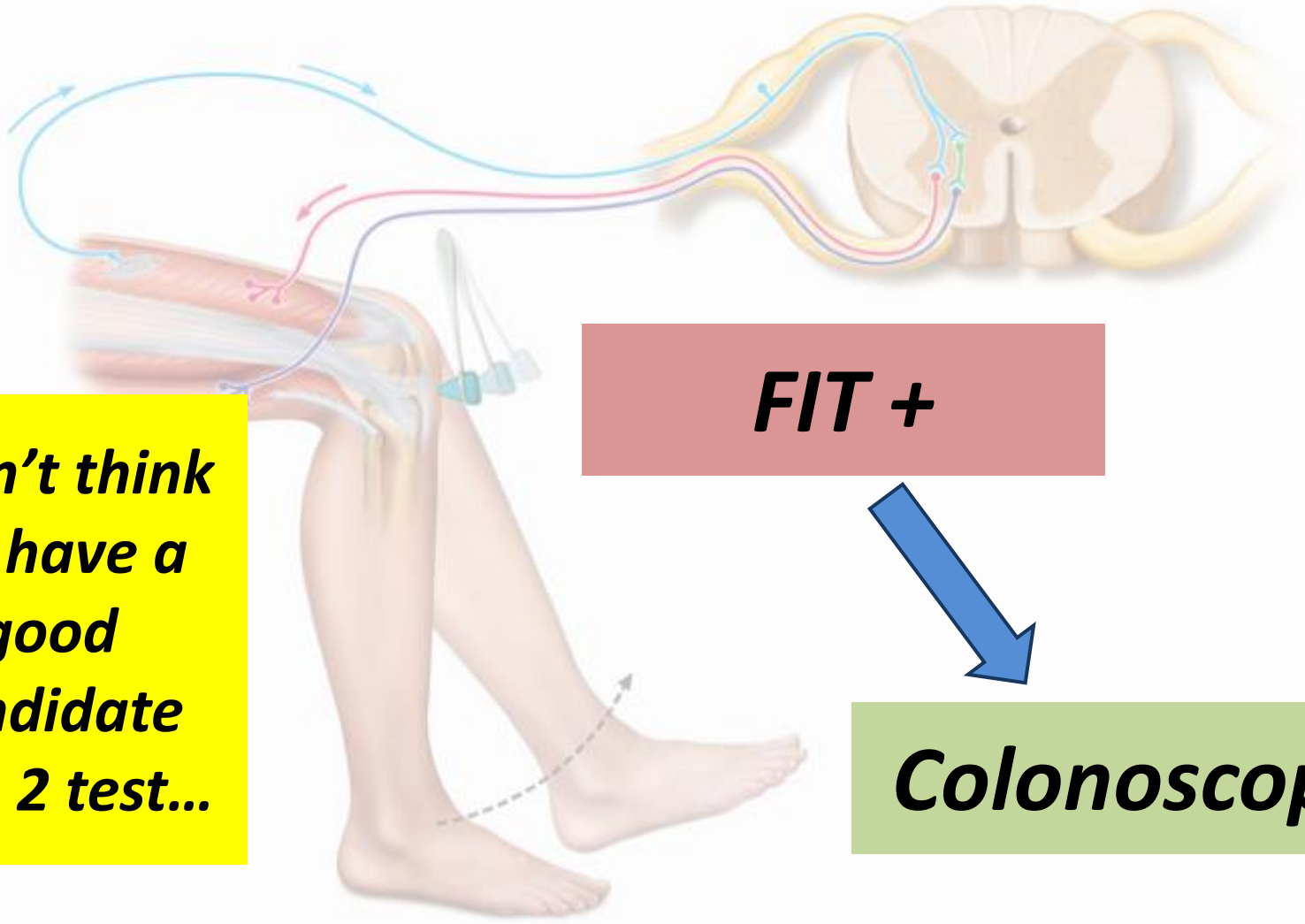
2014 study 73.8 (61.5–84.0)

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



I don't think we have a good candidate Step 2 test…

FIT +

Colonoscopy!

What if we ever got a fantastic Step 2 test?

What if we ever got a fantastic Step 2 test?

- *Why not use it as **Step 1** ?!?*

If we ever got this in Step 2, why not use it as **STEP 1 ?!?**

Step 1	Step 2	Step 3

- *Extremely high … n't lose cases)*
- *Hig… d out" fals…*
- *…in …*
- *[May … as in the general screen… population]*

Cost?
Access?
Infrastructure?
Other barriers?

Agenda

- Why my initial reflex reaction?
- What would be required of the second (triage) test before colonoscopy?
- Possible future steps

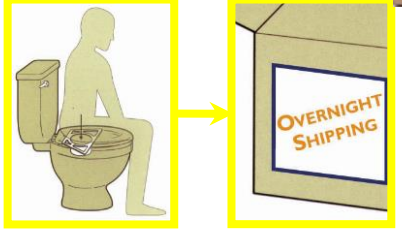
THE (possible) NEED:

- *Test 2 with very high sensitivity and specificity in FIT+*

NEED: Test 2 with high sensitivity and specificity in FIT+

Step 1

Step 2



Step 3

WE HAVE SUCH A TEST!

Step 1

Step 2

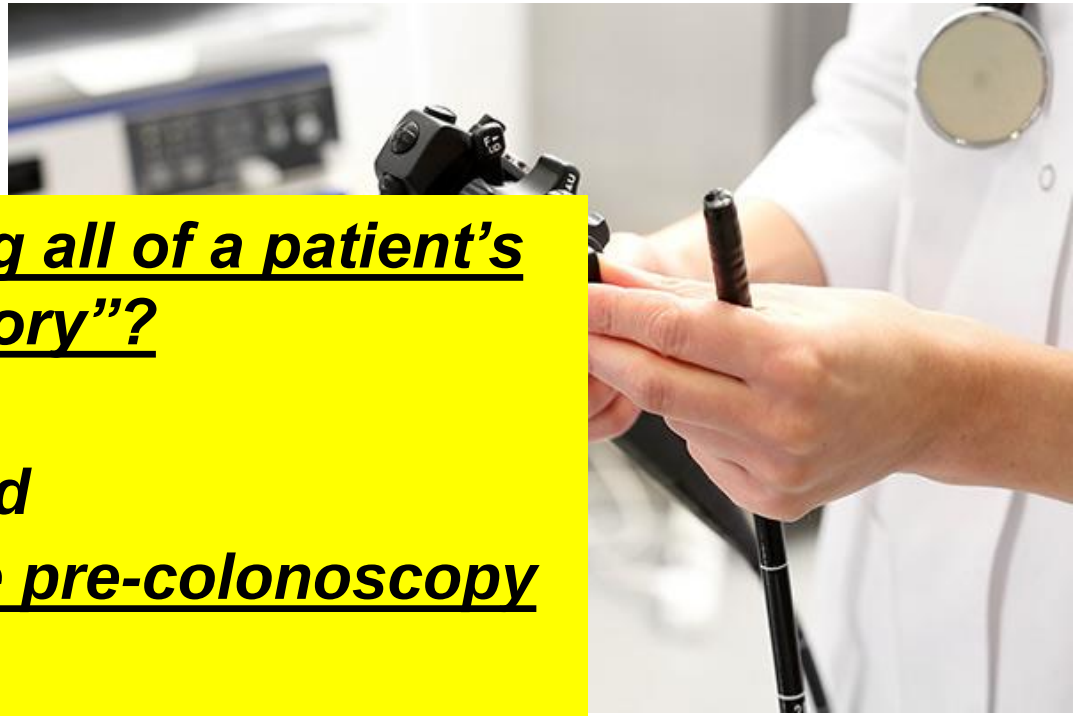
Step 3

Colonoscopy as Step 2 after OPTIMIZED FIT as Step 1?

Step 1

Step 2

Step 3 ~~Step 3~~



How about leveraging all of a patient's FIT "history"?

- ***# rounds of Hb=0***
- ***Hb>0, sub-threshold***
- ***FIT "history" as the pre-colonoscopy triage test?***

Final thought on 3-step vs. 2-step process

- The KISS principle
  - *"Keep it simple, stupid"*
- (The perfect is the enemy of the good)

Ladabaum and Ko, Clin Gastroenterol Hepatol 2023;21:3236

**** …with clever use of FIT history?***

WEO
The voice of world endoscopy

FIT positive: straight to colonoscopy* or a second test to increase specificity?

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