Update for the WEO Expert Working Group on New Test Evaluation:

Assessing the cost-effectiveness of new tests

May 20, 2022

Uri Ladabaum, M.D., M.S.
Professor of Medicine; Director, GI Cancer Prevention Program
Division of Gastroenterology and Hepatology
Stanford University School of Medicine

Commentary

Recommendations for a Step-Wise Comparative Approach to the Evaluation of New Screening Tests for Colorectal Cancer

Graeme P. Young, MD, FRACP, FTSE, AGAF[1]; Carlo Senore, MD, MSc[2]; Jack S. Mandel, PhD, MPH[3]; James E. Allison, MD, FACP, AGAF[4]; Wendy S. Atkin, MPH, PhD[5]; Robert Benamouzig, MD, PhD[6]; Patrick M. M. Bossuyt, PhD[7]; Mahinda De Silva, MB, BS, FRACP[8]; Lydia Guittet, MD, PhD[9]; Stephen P. Halloran, MBE, FRCPath[10]; Ulrike Haug, PhD[11]; Geir Hoff, MB, ChB, PhD[12]; Steven H. Itzkowitz, MD, FACP, FACG, AGAF[13]; Marcis Leja, MD, MBA, PhD, AGAF[14]; Bernard Levin, MB, BCh, FACP[15]; Gerrit A. Meijer, MD, PhD[16]; Colm A. O'Morain, MD[17]; Susan Parry, MbCHB, FRACP18[18]; Linda Rabeneck, MD, MPH, FRCPC[19]; Paul Rozen, MD[20†]; Hiroshi Saito, MD, PhD[21]; Robert E. Schoen, MD, MPH[22]; Helen E. Seaman, BSc, PhD[23]; Robert J. C. Steele, MD, FRCS[24]; Joseph J. Y. Sung, MD, PhD[25]; and Sidney J. Winawer, MD[26]

Cancer March 15, 2016

Requirements for new screening tests

- "*Comparing new CRC screening tests using CRC mortality as the endpoint will probably never be feasible on the grounds of size, time, and cost*."
- Simpler studies: surrogate endpoints (e.g. CRC or AA detection) with proven comparator

Young et al., Cancer 2016; 122(6): 826

Four phases

Phase	Nature	Cost/ modeling?
1		
2		
3		
4		

Young et al., Cancer 2016; 122(6): 826

Four phases

Phase	Nature	Cost/ modeling?
1	Retrospective: CRC vs. normal	
2	Prospective: Lesions along neoplasia continuum	
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4		

Young et al., Cancer 2016; 122(6): 826

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Phase	Nature	Cost/ modeling?
1	Retrospective: CRC vs. normal	
2	Prospective: Lesions along neoplasia continuum	
3	Single round of screening	
4	Program, multiple rounds	

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Four phases

Phase	Nature	Cost/ modeling?
1	Retrospective: CRC vs. normal	
2	Prospective: Lesions along neoplasia continuum	
3	Single round of screening	Initial CEA
4	Program, multiple rounds	Refined CEA

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Four phases

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2021-22 New tests comparison Consensus Process

- Delphi process, 3 rounds, 12 principles
- Principle 4: **Predicting value by paired comparison to a proven test**
  - *"Intermediate endpoints known to reliably and consistently predict potential for reducing CRC mortality and/or incidence …to compare a new with existing tests"*
  - Modeling as progress from Phase 1 to 4?

G. Young, C. Senore, R. Bresalier et al., Work in Progress

The challenges posed by Graeme Young

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Early-stage proxies / surrogates for:

- Long-term effectiveness?

The challenges posed by Graeme Young

Early-stage proxies / surrogates for:

- Long-term effectiveness? (GY: “NNS”?)

NNS = “number needed to scope” to detect 1 CRC/APL

The challenges posed by Graeme Young

Early-stage proxies / surrogates for:

- Long-term effectiveness?
- Programmatic cost-effectiveness?

Blood-based biomarkers for CRC screening

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

Calculating possible Round 1 surrogate markers

Test	Sens CRC	Sens APL	Sens NAA	Spec = 1- FP in normal	Interval	Test cost

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Prevalence as in Imperiale*	CRC	APL	NAA	Normal	Total cohort
					10,000

* Imperiale *et al*, NEJM 2014; 370:1287

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	Detected/Sent to colonoscopy				No colo	Surrogate
n						NNS/CRC,APL
Cost						Cost/CRC,APL

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Cost	FIT + Colo Tx			FIT + Colo Dx	FIT	Cost/CRC,APL

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FIT	0.74	0.24	0.08	0.96	(1)	$18

Prevalence as in Imperiale*	CRC	APL	NAA	Normal	Total cohort
	65	758	2,896	6,281	10,000

	Detected/Sent to colonoscopy				No colo	Surrogate
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	Detected/Sent to colonoscopy				No colo	Surrogate
n	48	182	232	251	9,287	NNS/CRC,APL
Cost	FIT + Colo Tx			FIT + Colo Dx	FIT	Cost/CRC,APL

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	Detected/Sent to colonoscopy				No colo	Surrogate
n	**48**	**182**	232	251	9,287	NNS/CRC,APL **3.1**
Cost	FIT + Colo Tx			FIT + Colo Dx	FIT	Cost/CRC,APL **$3,800**

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NNS = "number needed to scope"

Explore proxies / surrogates across a set of possible screening tests

(compare with long-term estimates in our decision analytic model*)

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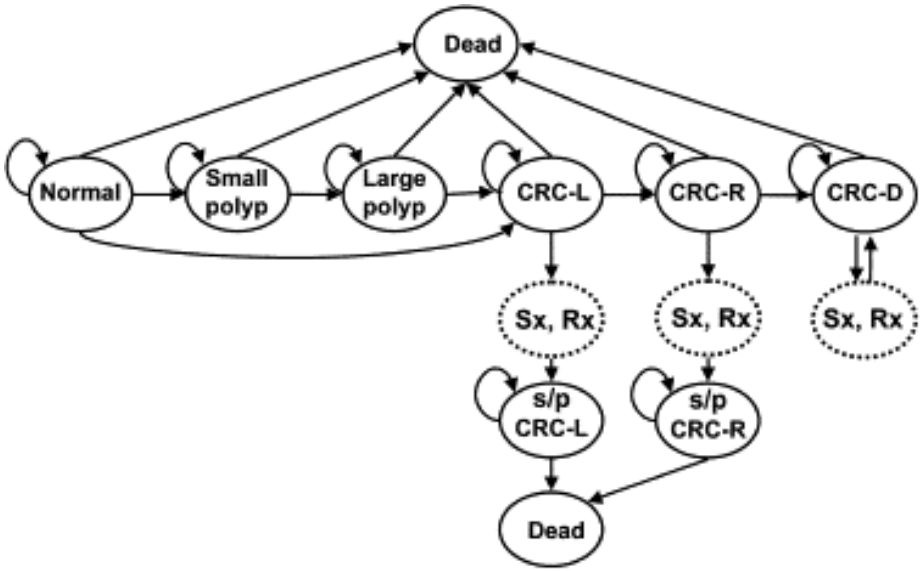

*Recent applications:

- *Cost-effectiveness of screening at 45*
- *Consequences of CMS coverage decision on blood-based biomarkers*

Ladabaum et al, Gastroenterology 2019;157:137
Ladabaum et al, JNCI 2022; PMID: 35134969

Test attributes

Test	Sens CRC	Sens APL	Sens NAA	Spec = 1- FP in normal	Interval	Test cost
FIT	0.74	0.24	0.08	0.96	1	$18
CMS minimum						
CMS “plus”						
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High sens / high spec						
Colo						
FIT-DNA						

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Colo	0.95	0.9	0.85	1	10	$740 Dx, $1,083 Tx
FIT-DNA	0.92	0.42	0.17	0.9	3 (1)	$509 ($100)

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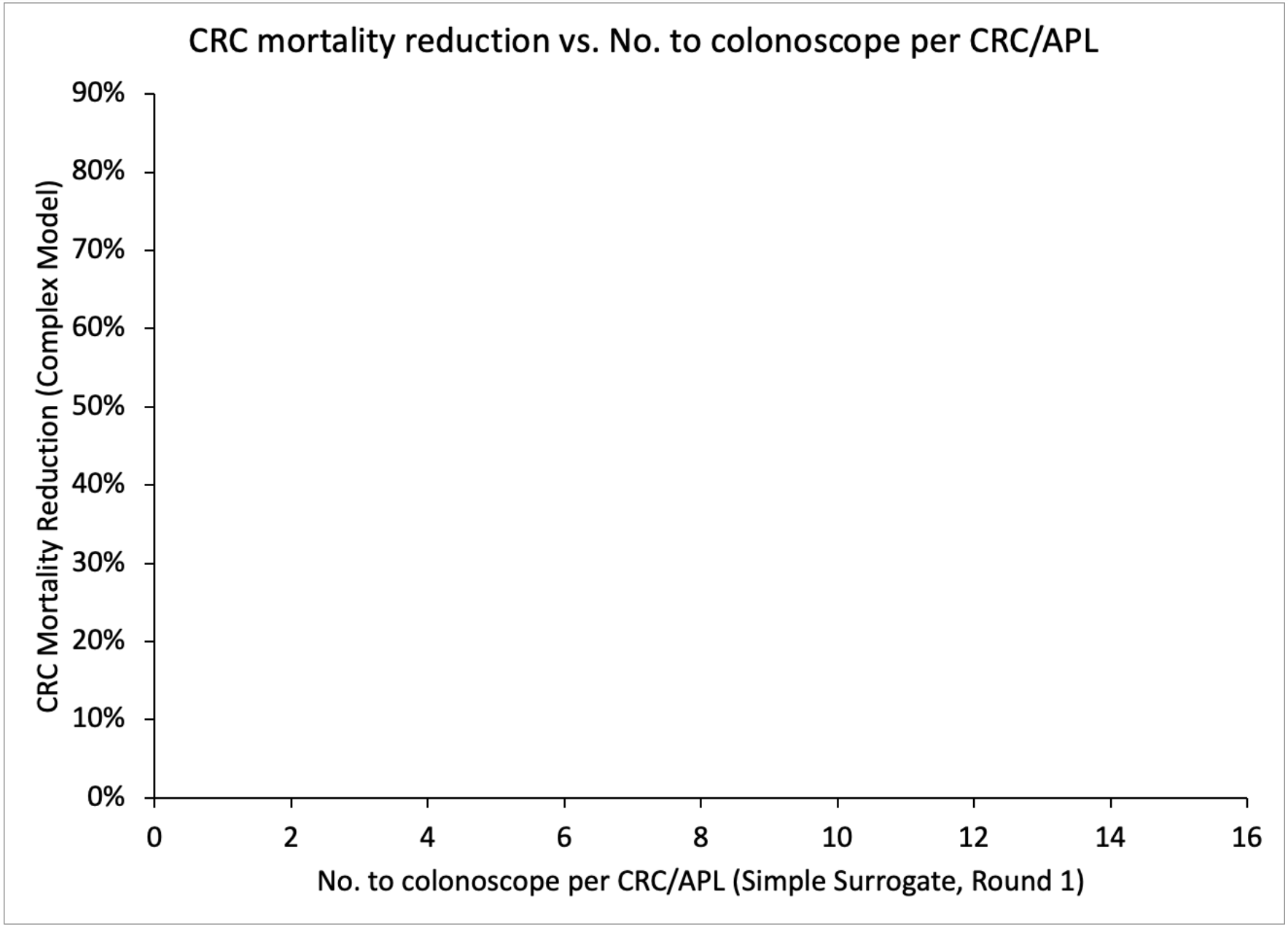
A proxy for long-term effectiveness?

No. needed to scope for 1 CRC/APL (Round 1)



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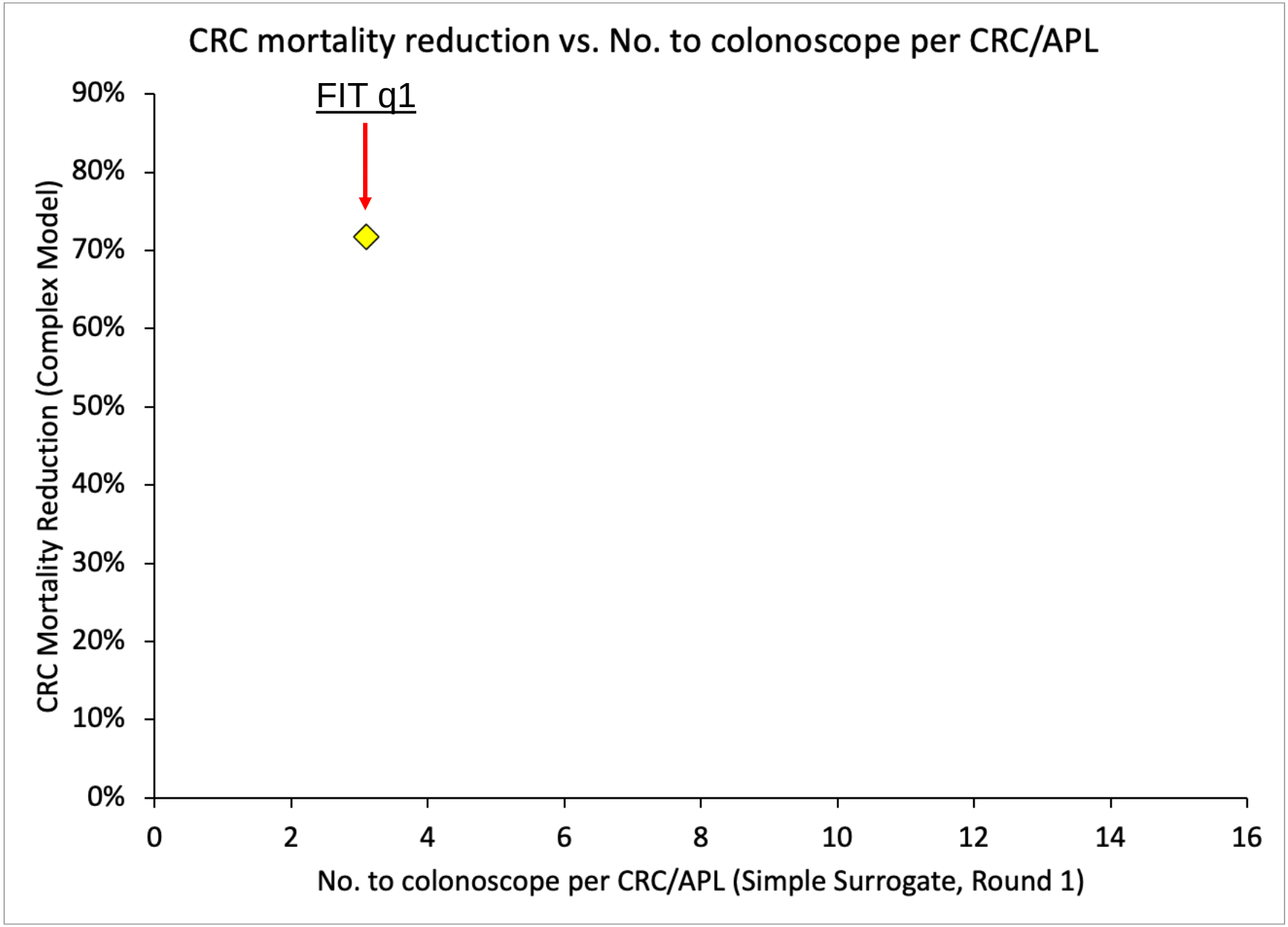

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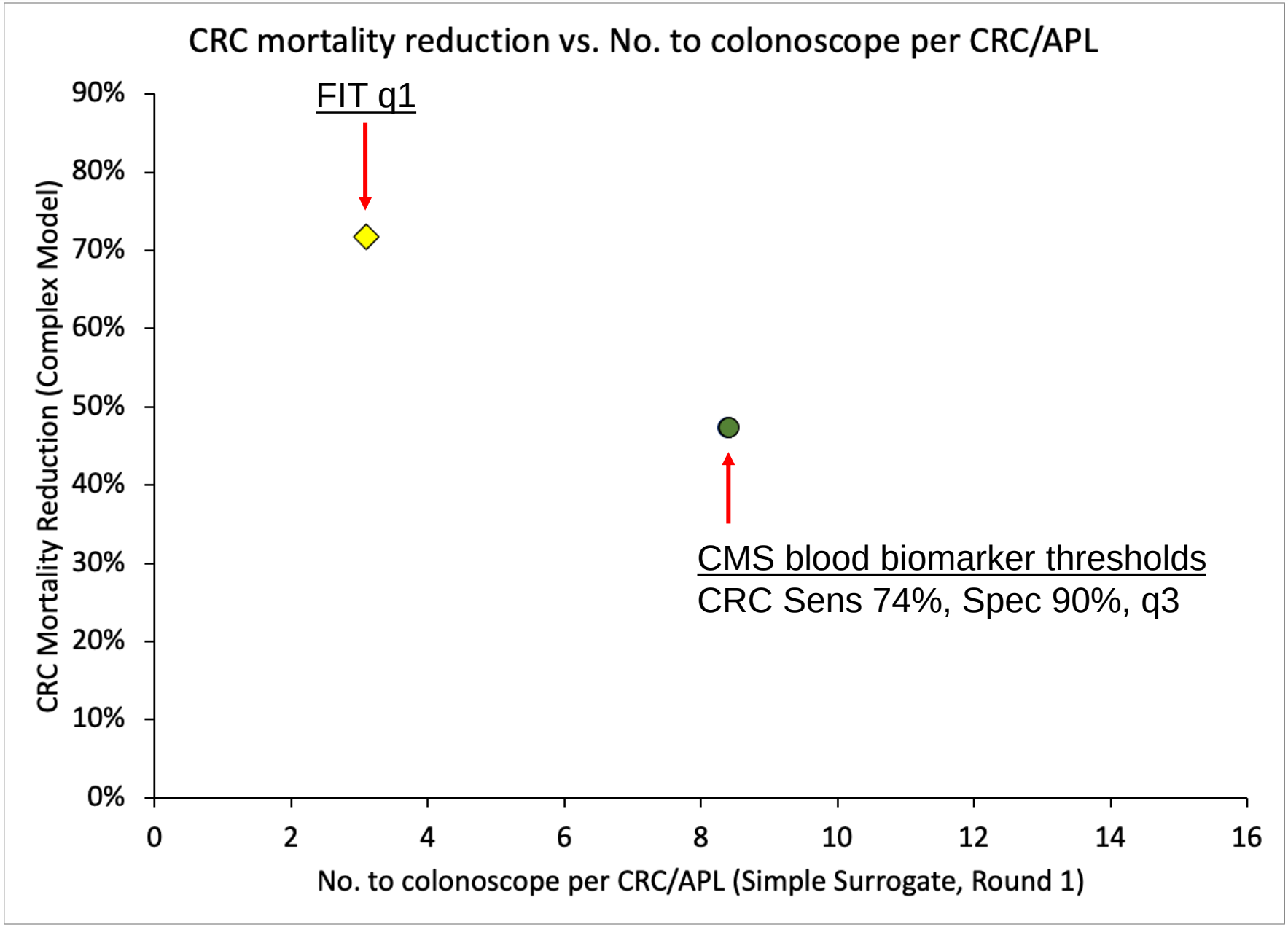

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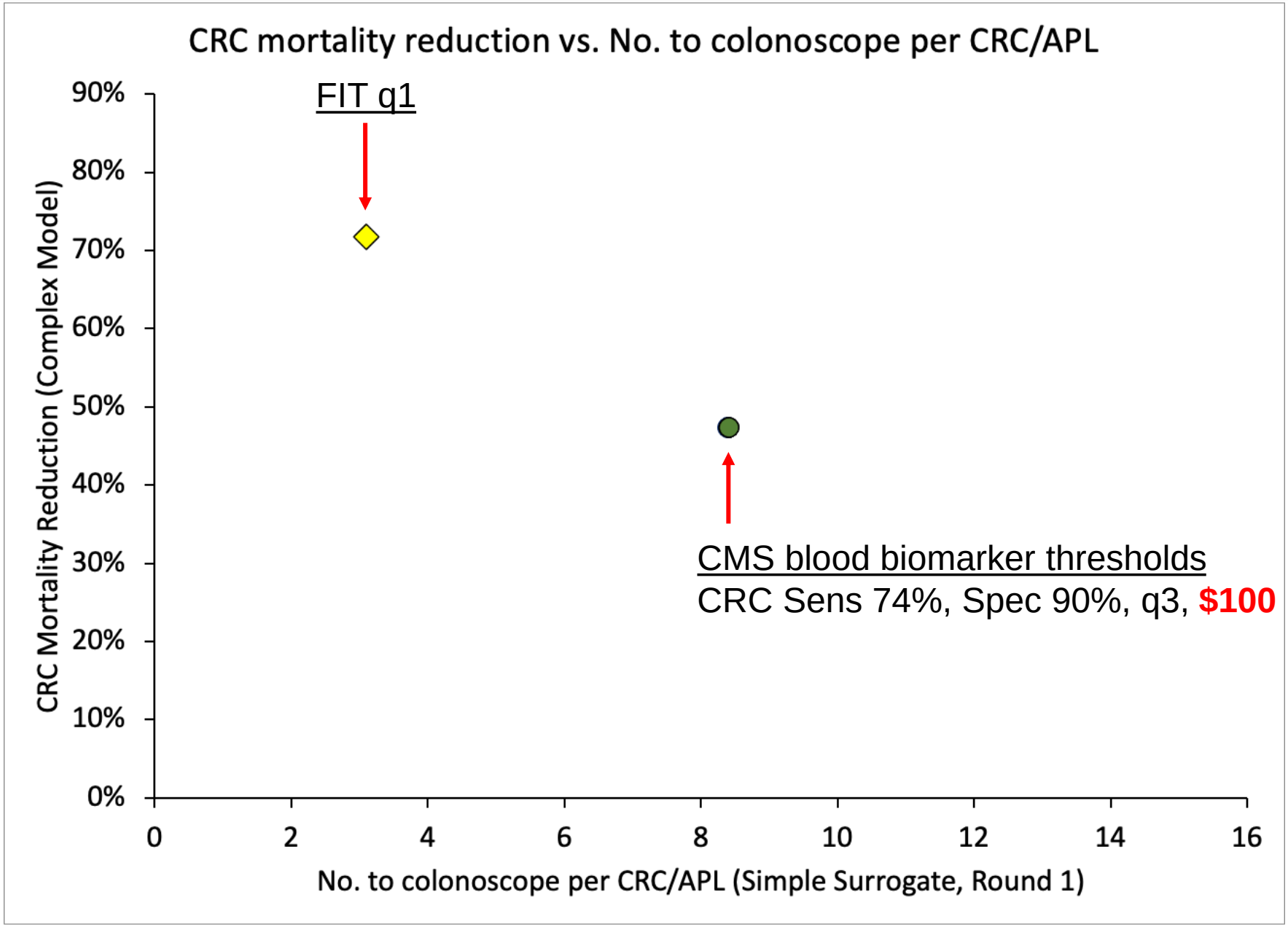

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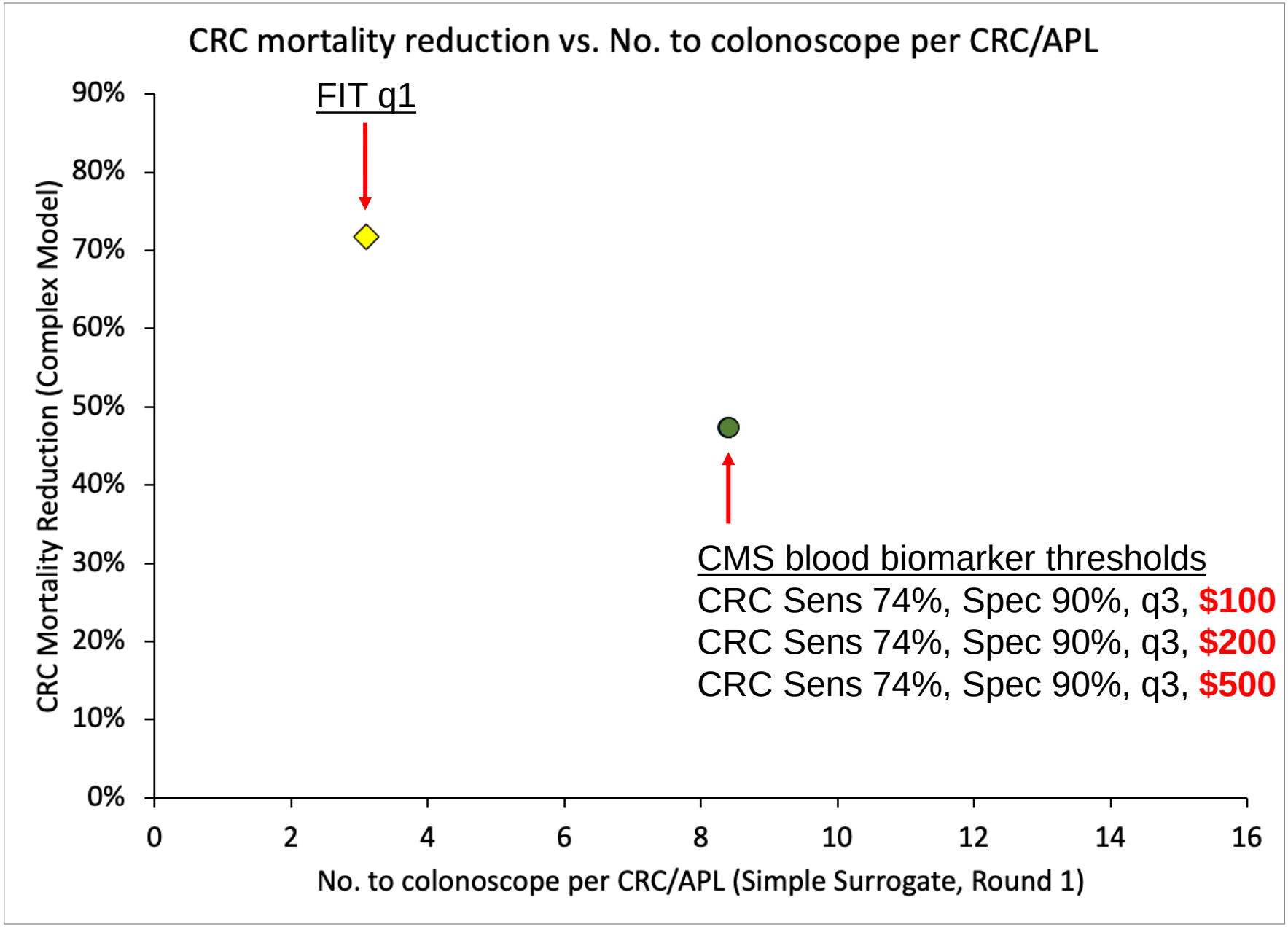

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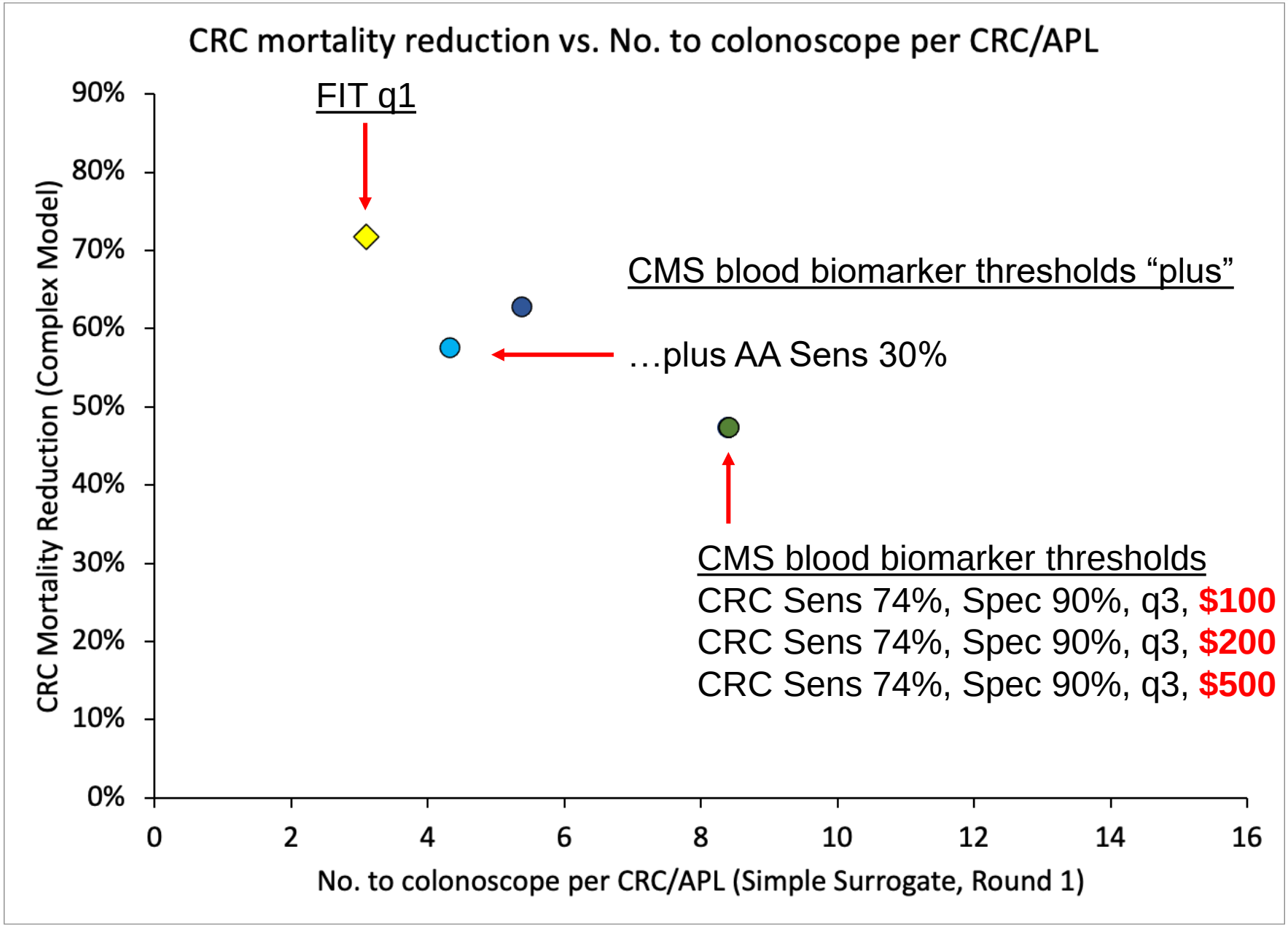

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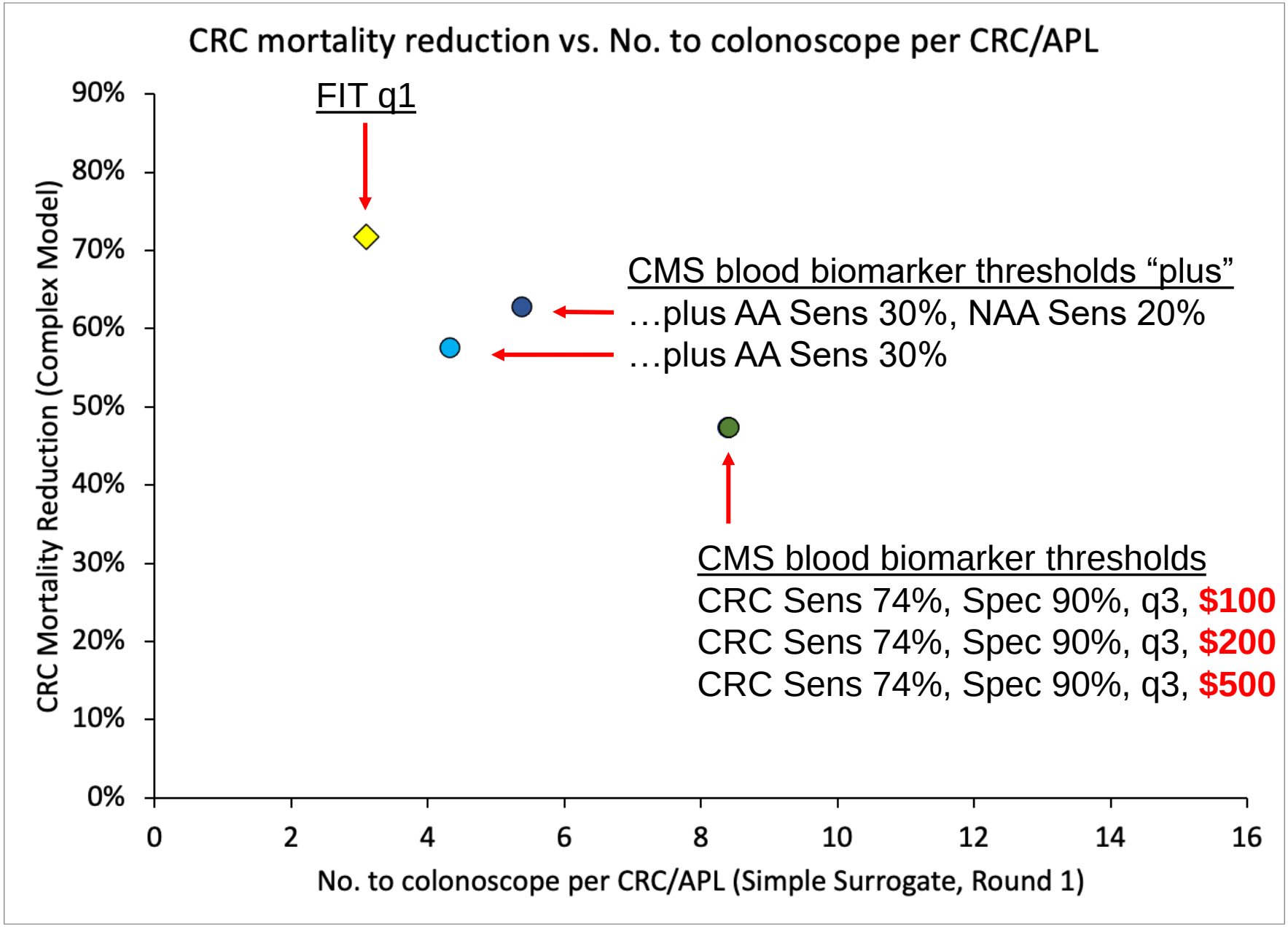

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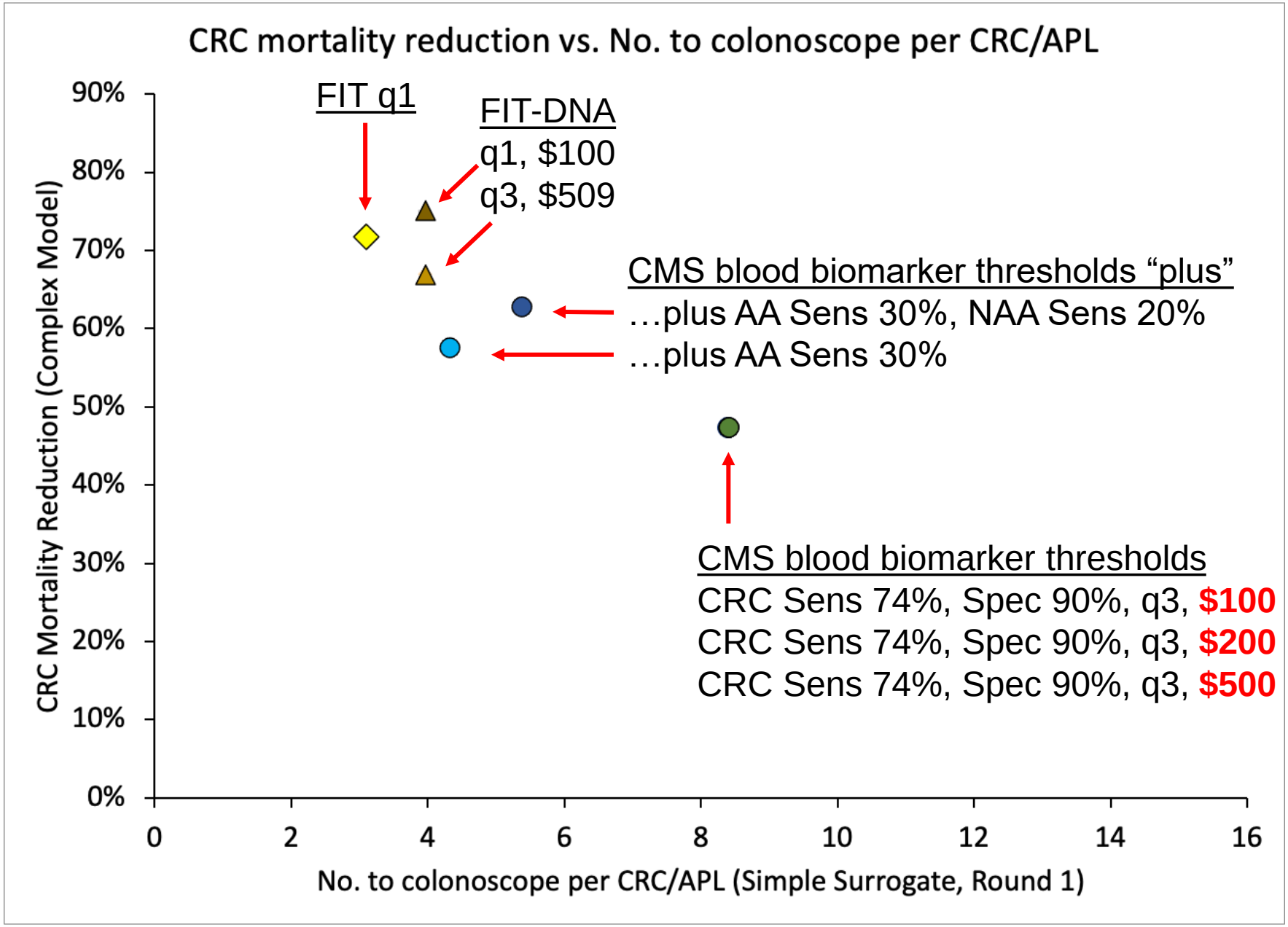

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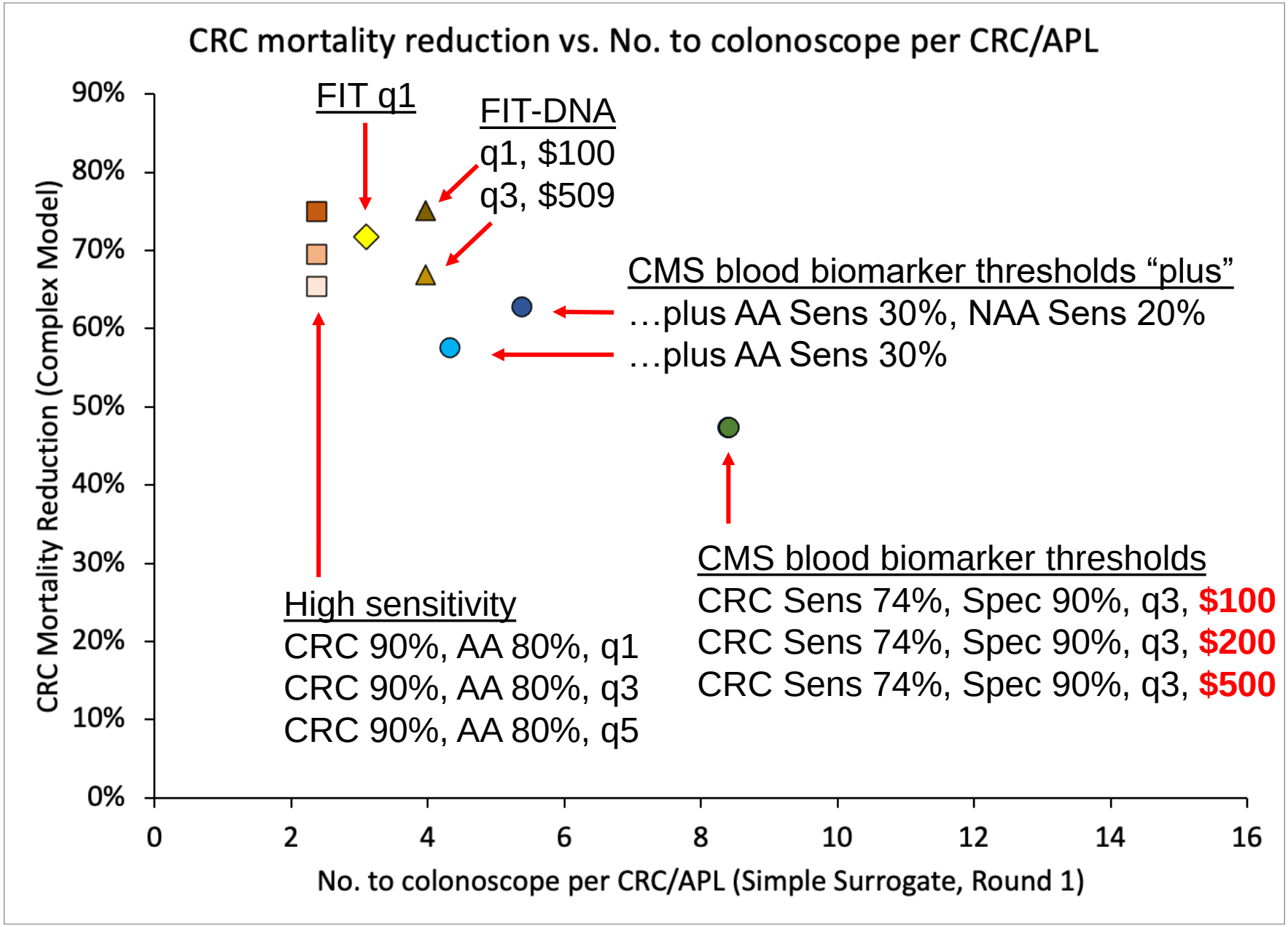

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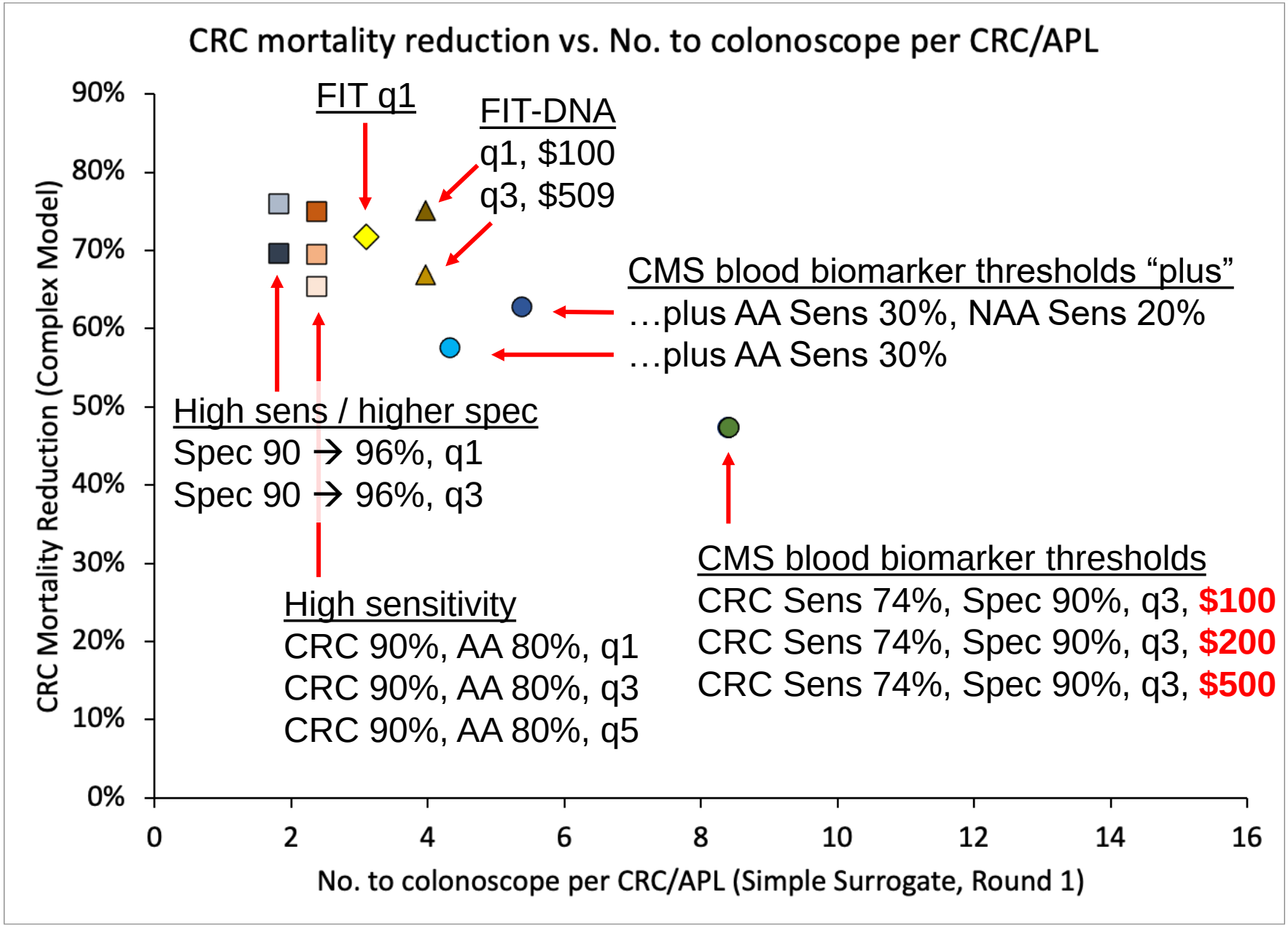

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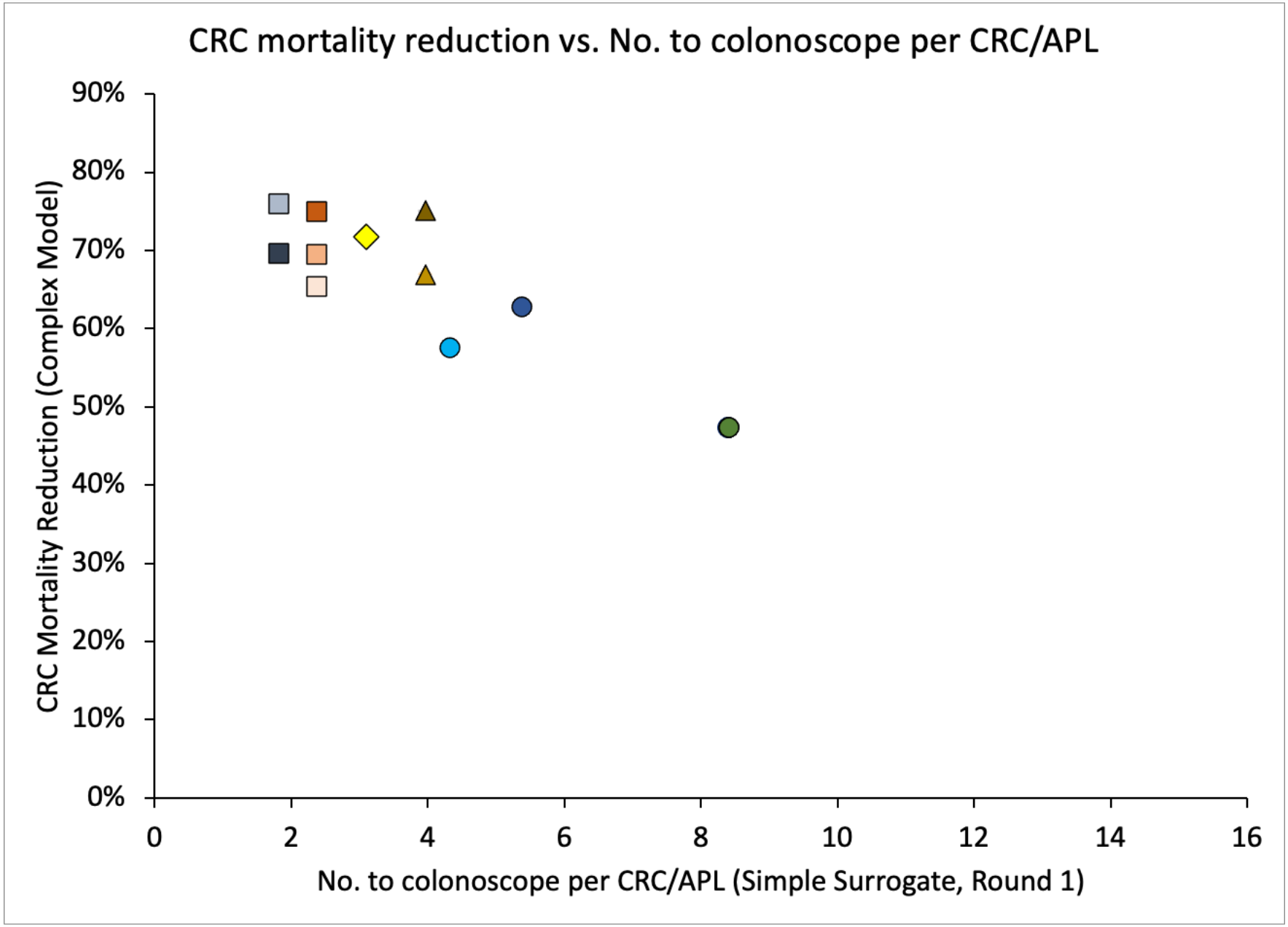

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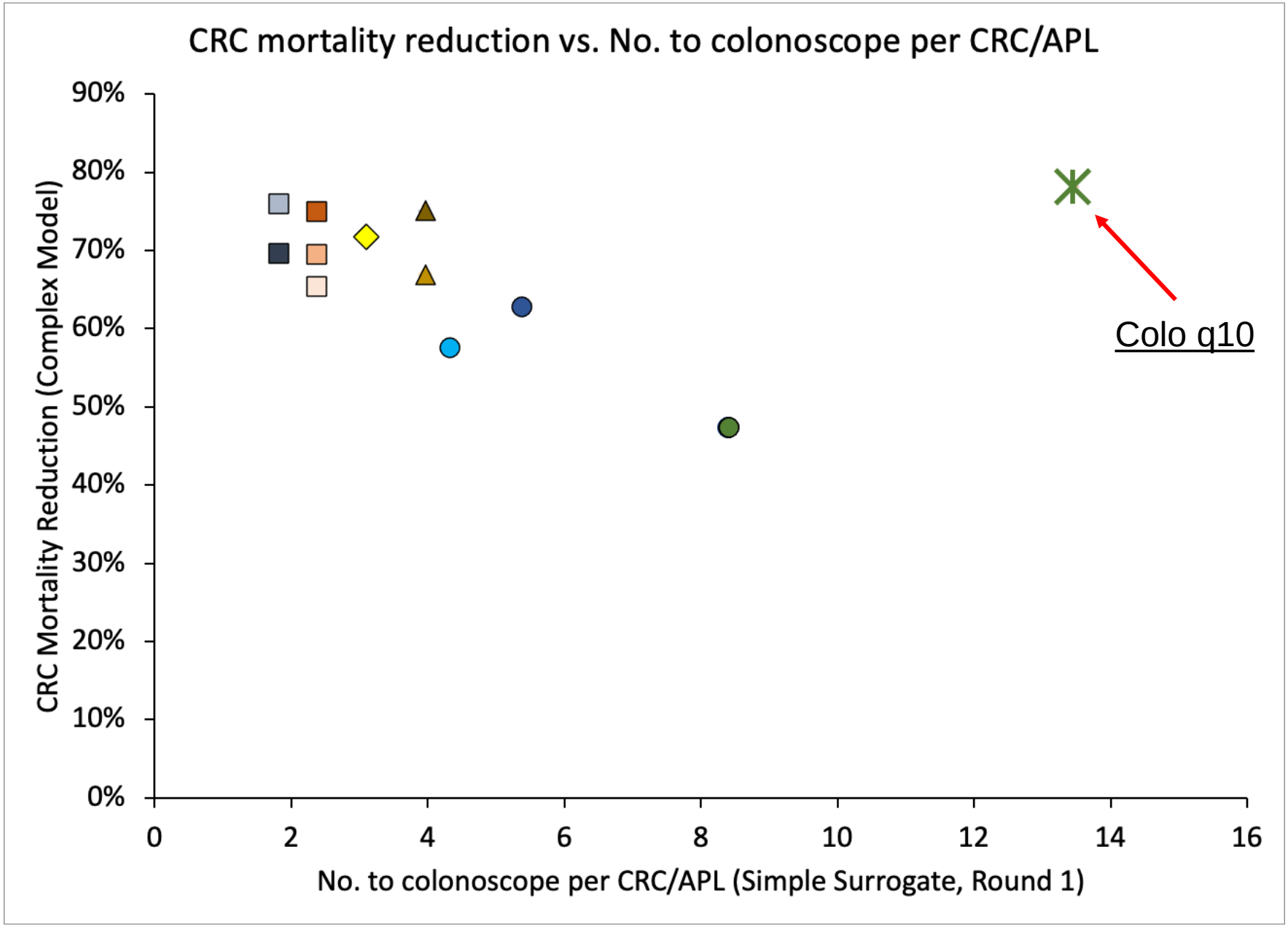

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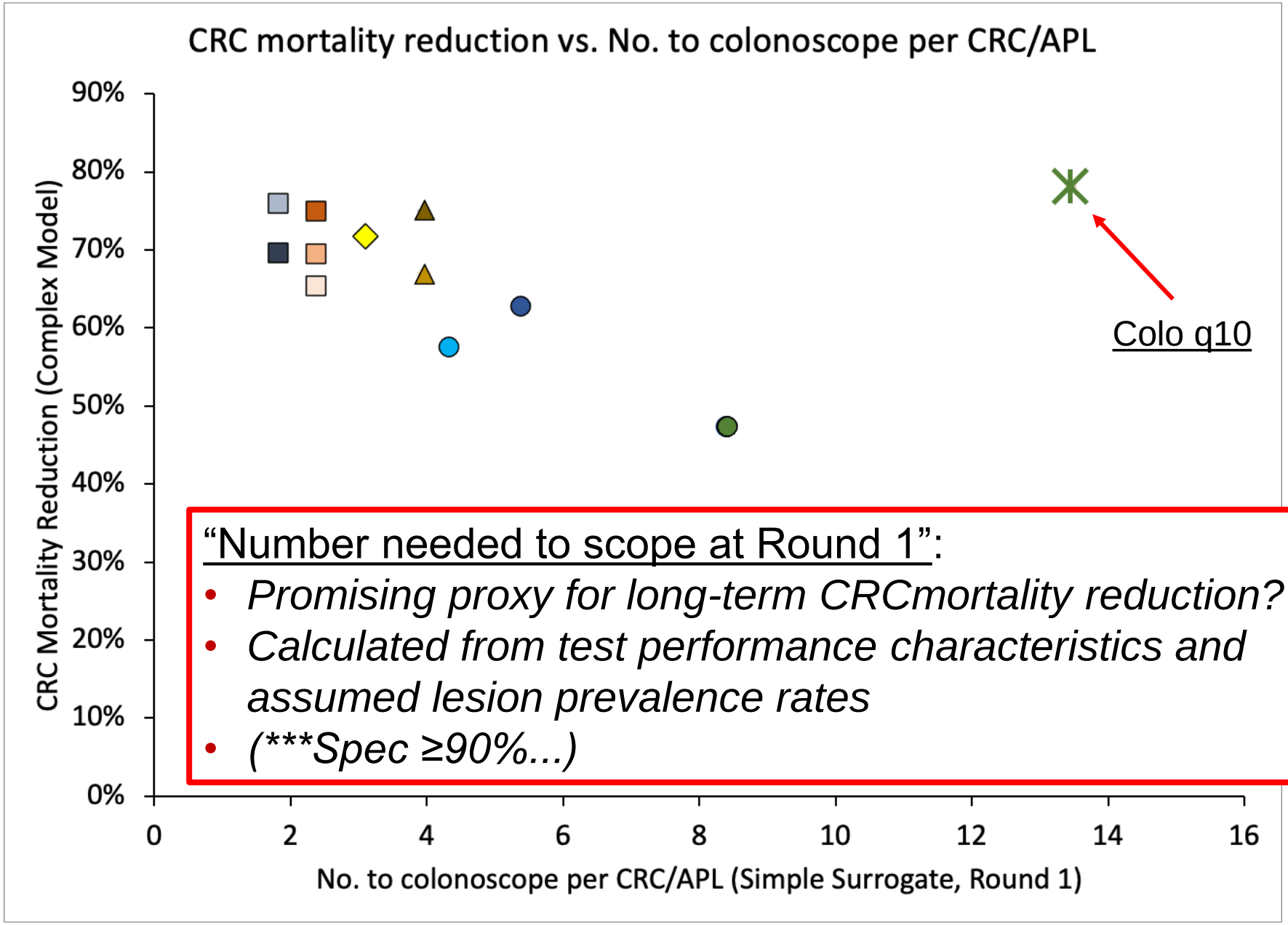
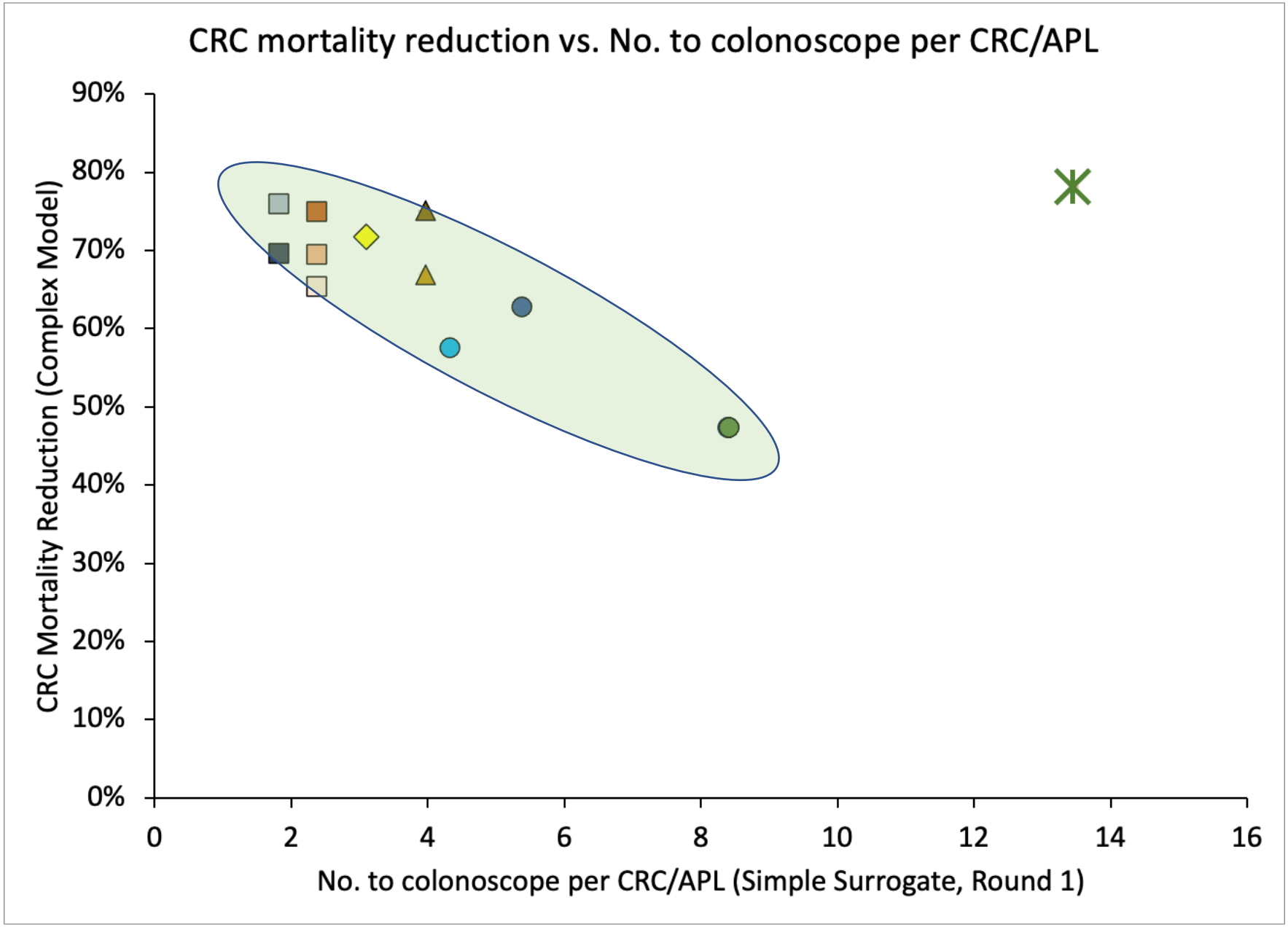


Falls apart with Spec < 90%



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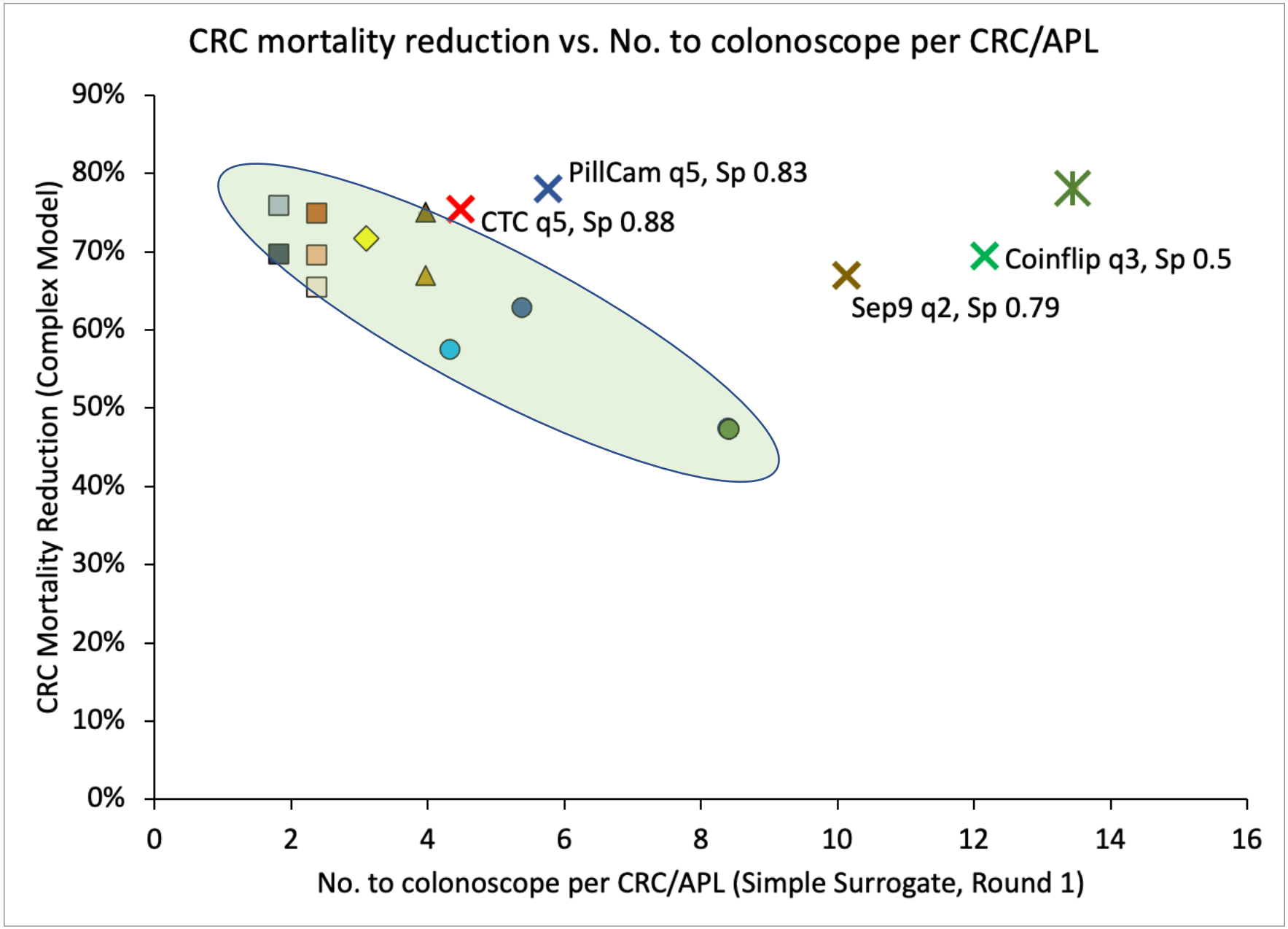
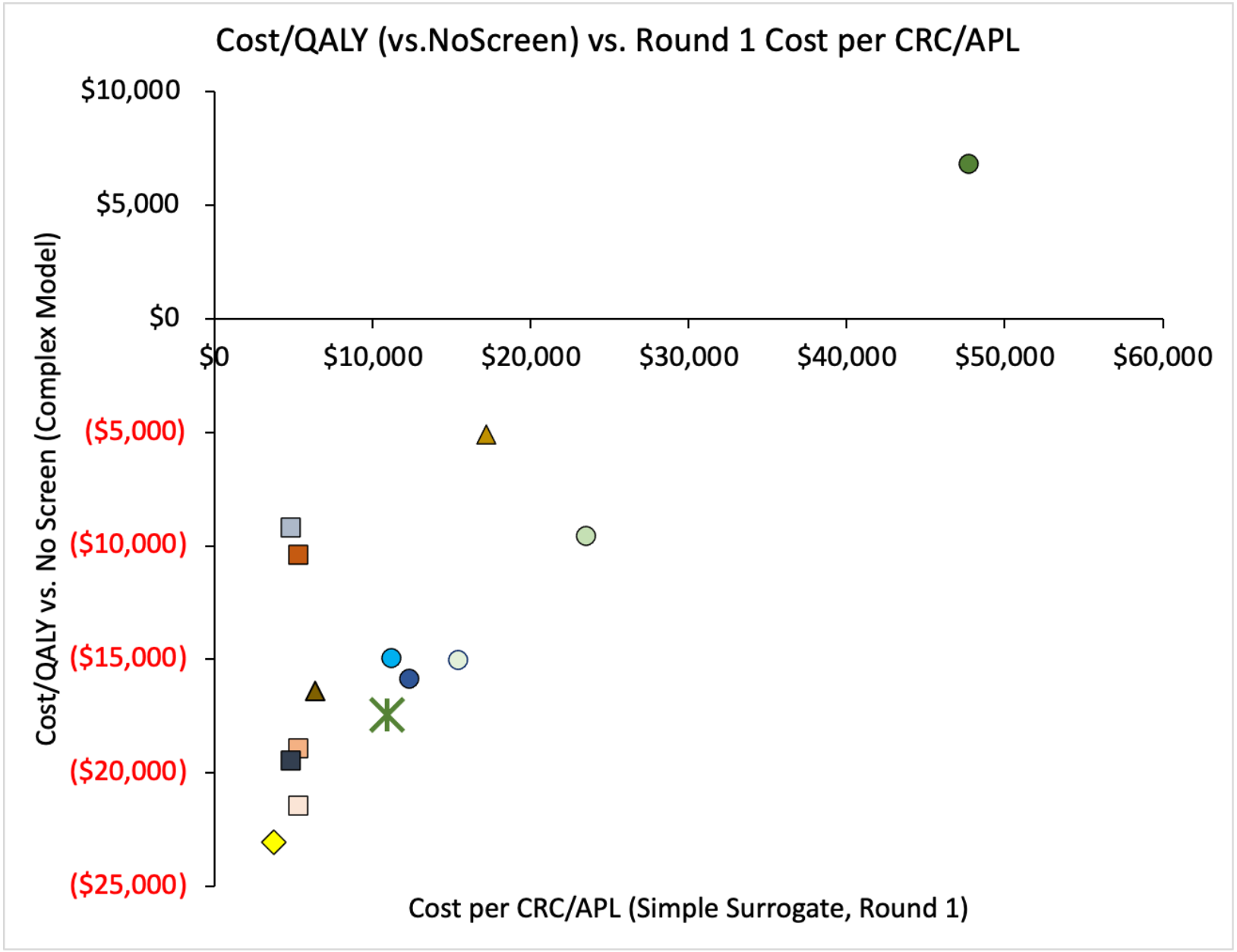


A proxy for cost-effectiveness?

Cost per CRC/APL detected (Round 1)



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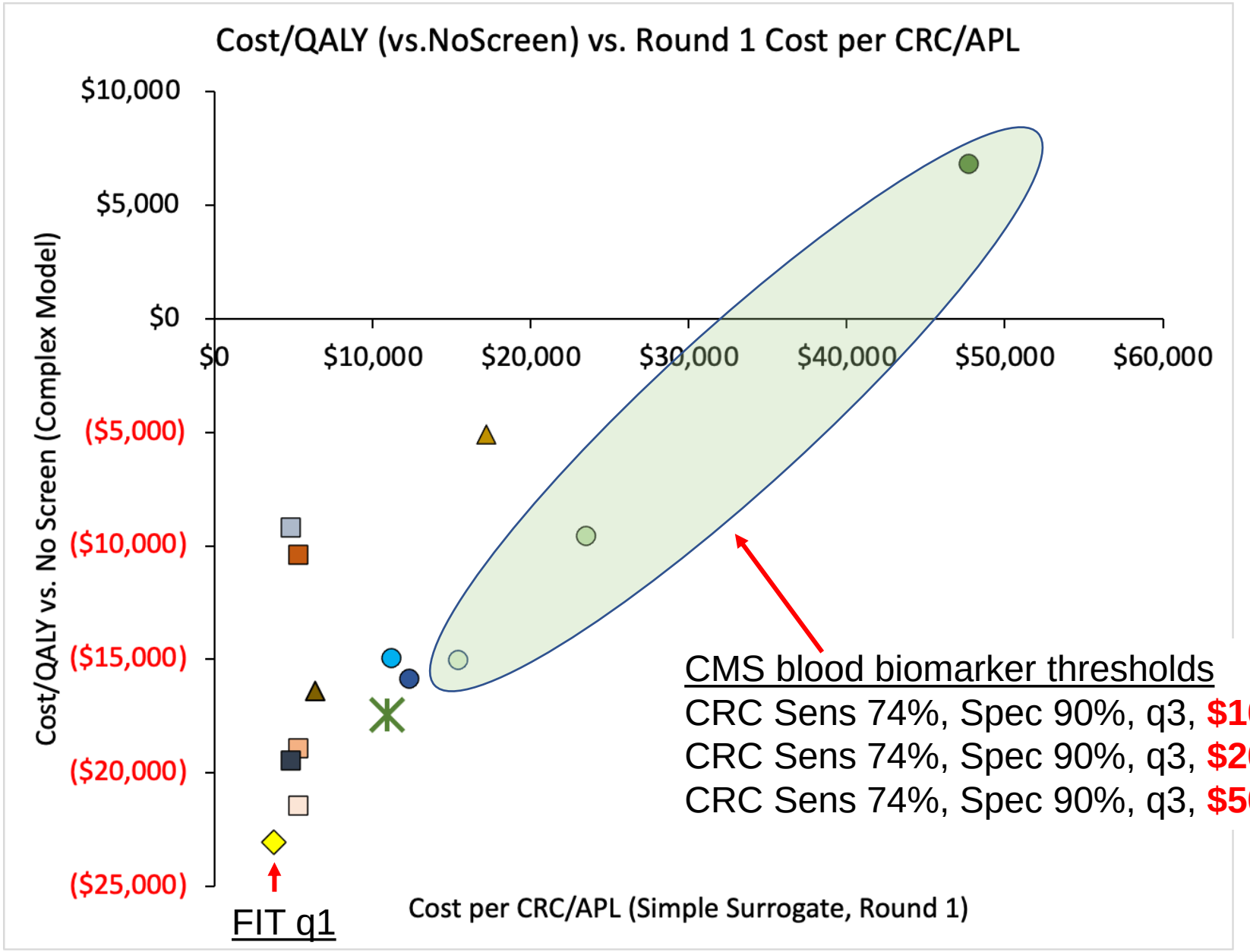

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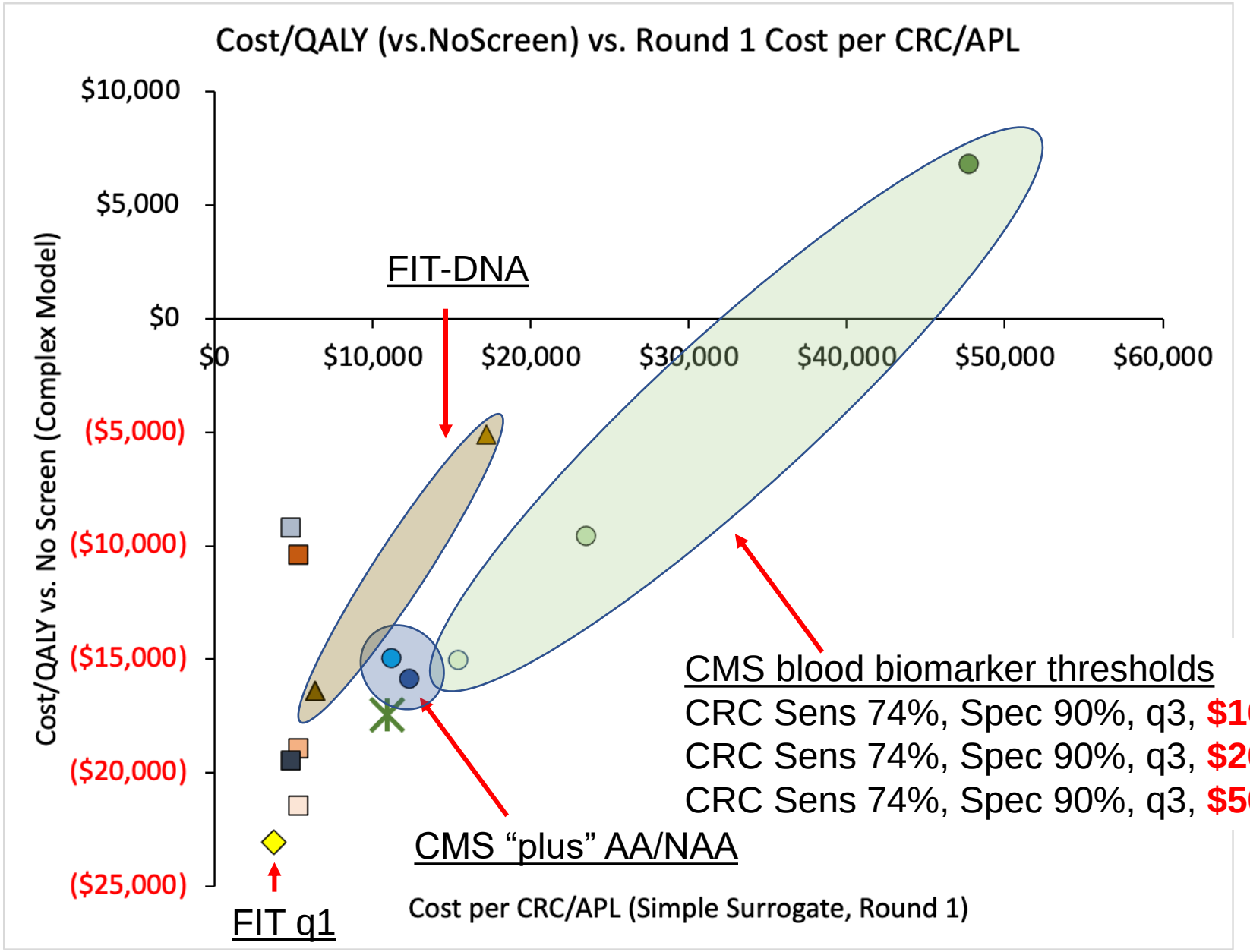

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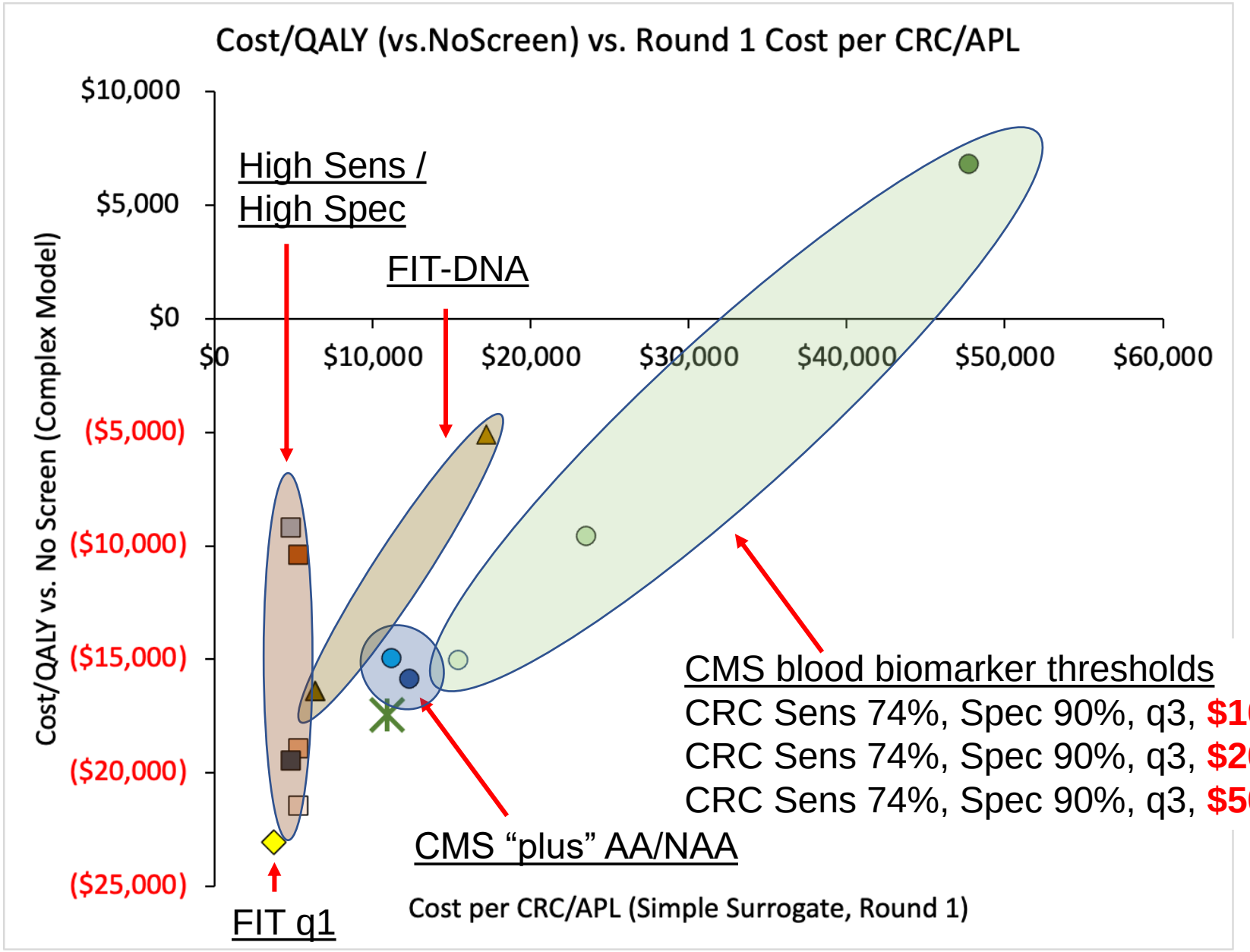

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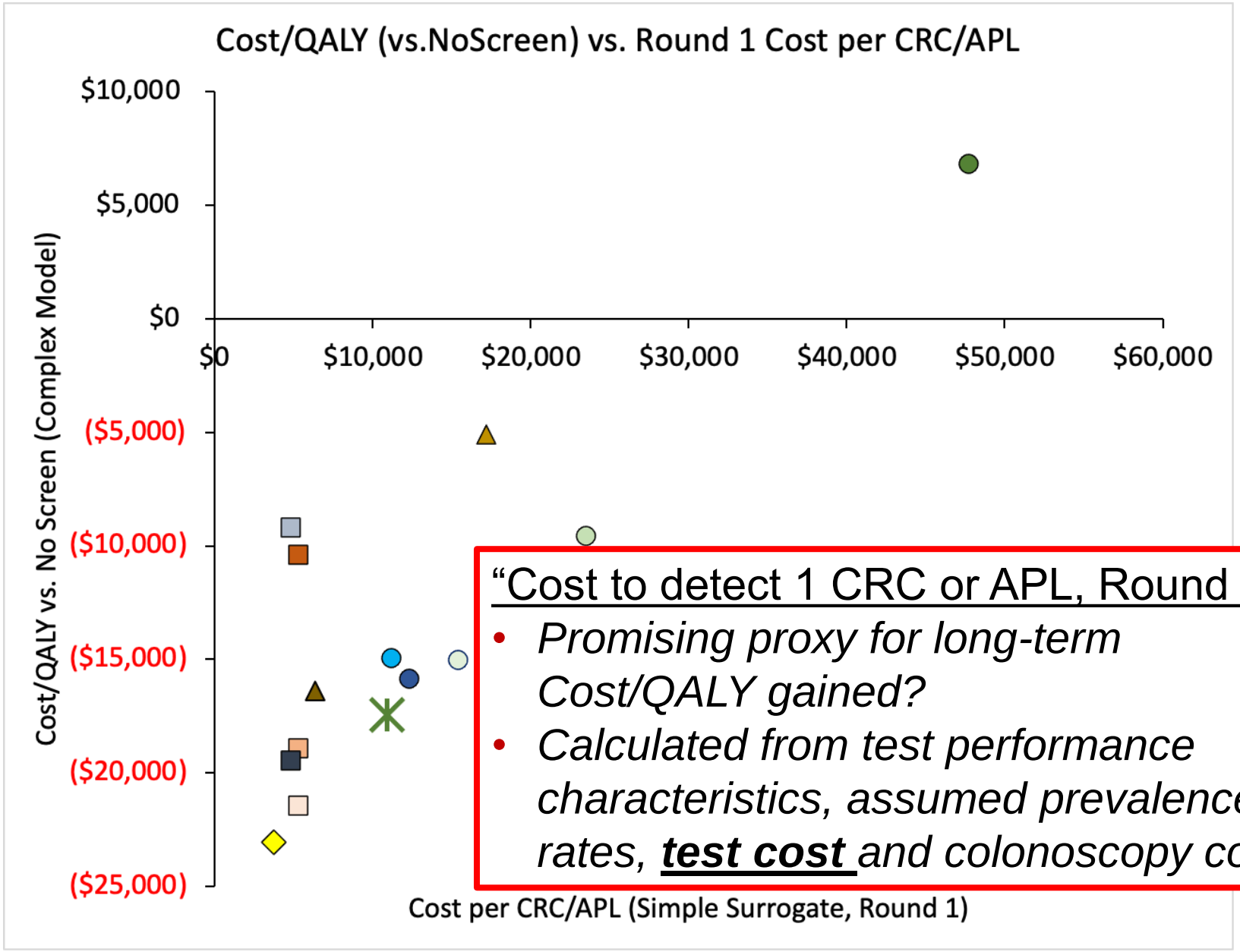

"Cost to detect 1 CRC or APL, Round 1":

- *Promising proxy for long-term Cost/QALY gained?*
- *Calculated from test performance characteristics, assumed prevalence rates, **test cost** and colonoscopy cost*

The challenges posed by Graeme Young

Based on limited exploration, there ***<u>may be</u>*** early-stage proxies / surrogates for:

- Long-term effectiveness
- Programmatic cost-effectiveness

A simple calculator in Excel for Round 1 proxies

Test	Sens CRC	Sens APL	Sens NAA	Spec = 1- FP in normal	Interval	Test cost	Colo Dx	Colo Tx
FIT	*0.74*	*0.24*	*0.08*	*0.96*	1	*$18*	*$740*	*$1,083*

Prevalence	CRC	APL	NAA	Normal	Total cohort
as in Imperiale*	65	758	2,896	6,281	10,000

	CRC	APL	NAA	Normal	No scope	NNS for 1 CRC/APL	Cost for 1 CRC/APL
Detected/to colo	48	182	232	251	9,287	**3.1**	
Cost	$52,958	$200,294	$255,080	$190,440	$167,167		**$3,765**

* Prevalence as in Imperiale *et al*, NEJM 2014; 370:1287

As tests are being developed (Phases 1,2)

- Exploratory cost-effectiveness analyses? (thought experiment; high uncertainty)
- *Proxy measures?*
- Must NOT stifle innovation
- Usually not yet anchored in early phases:
  - Sensitivity vs. specificity trade-offs
  - Test cost
  - Test interval
  - *Permutations: performance, cost, interval*
  - *Participation? Outreach costs?*

Beyond the Consensus Delphi Process

- Test proxy measures in other models?
- Formally calculate correlation coefficients?
- Are proxy measures better than “general gestalt”?
- Who is the audience at each phase?
  - Test developers / industry?
  - Screening program directors?
  - Budget managers?
  - *When does it matter?*

Discussion: NNS/CRC,APL & Cost/CRC,APL Round 1