Supplement 1. More details on model used in the main text

In this Supplement, we model goals for a hypothetical, rational individual who seeks to maximize the expected benefit of screening. We adopt the following notation:

$B =$ Benefit of screening

$LY =$ Life-years, $LE =$ Life expectancy

$d =$ Disease, $nd =$ No disease

$s =$ Screening, $ns =$ No screening

$p =$ Probability of disease

$\gamma =$ Stage of disease (local, regional, distant/metastatic, unstaged)

$\kappa =$ Probability of complications from screening

$\pi_{a|a_0} =$ Probability of survival to age a, conditional on survival to age a_0

$DF =$ Discount factor

$E =$ Expected value

$RRR_I =$ Relative risk reduction of screening on disease incidence

Goals for a rational individual contemplating disease screening. We defined the benefit of screening as the increase in utility from additional life-years lived due to screening: $B = u(\mathrm{LY}_s) - u(\mathrm{LY}_{ns})$. We then considered a rational individual who sought to maximize the expected benefit of screening by choosing an optimal age of screening initiation, screening frequency, and age of screening cessation: $max_{A_0,\mathrm{f},A_1} E[B] = E[u(\mathrm{LY}_s)] - E[u(\mathrm{LY}_{ns})]$, where a_0=age of screening initiation, f=screening frequency, a_1= age of screening cessation.

The expected benefit of screening was a weighted probability of the utility of life expectancy in 4 states: disease with screening, no disease with screening, disease without screening, and no disease without screening. Disease was further stratified by stage (local, regional, distant/metastatic, and unstaged). Additionally, the individual had a small probability (κ) of fatal complications, in which case he/she would lose all life expectancy that would have occurred in the absence of screening. Mathematically:

$$E[B] = \sum_{a=a_0}^{\infty} \frac{\pi_{a|a_0}}{(1+DF)^a} \left(\left\{ \sum_\gamma p_{\gamma,s,a} \cdot \underbrace{u\left(LE_{s,a|d,\gamma}\right)}_{\text{disease with screening}} \right\} + \left(1 - \sum_\gamma p_{\gamma,s,a}\right) \cdot \underbrace{u\left(LE_{s,a|nd}\right)}_{\text{no disease with screening}} - \right.$$

$$\left. \underbrace{\kappa \cdot u\left(LE_{ns,a}\right)}_{\text{risk of complications}} - \left[\left\{ \sum_\gamma p_{\gamma,ns,a} \cdot \underbrace{u\left(LE_{ns,a|d,\gamma}\right)}_{\substack{\text{disease without} \\ \text{screening}}} \right\} + \left(1 - \sum_\gamma p_{\gamma,ns,a}\right) \cdot \underbrace{u\left(LE_{ns,a|nd}\right)}_{\substack{\text{no disease without} \\ \text{screening}}} \right] \right) \text{ in years}$$

with screening ($a \leq a_1$ and $(a - a_0) \bmod f = 0$) and zero otherwise.

Assumptions. Given the low prevalence of disease in the general population, we assumed that life expectancy with no disease would equal life expectancy in the general population; that is, $LE_{s,a|nd} \approx LE_{ns,a|nd} \approx LE_{ns,a} \approx LE_a$. Second, we assumed that, at each age, the probability of disease with screening (across stages) could be expressed as the probability of disease without screening multiplied by a relative risk reduction for disease incidence (I), so that $\sum_\gamma \mathrm{p}_{\gamma,\mathrm{s,a}} = \mathrm{p}_{\mathrm{ns,a}} \cdot \mathrm{RRR}_\mathrm{I}$.

Life expectancy conditional on disease and screening status. Due to early detection of tumors, life expectancy may be longer in diseased individuals who received cancer screening, as compared with diseased individuals who did not receive cancer screening. Therefore, we estimated life expectancy conditional on disease and screening status, using published data on

relative survival probabilities and colorectal cancer screening rates. In particular, we modeled overall relative survival probabilities as a weighted average of probabilities for individuals who did versus did not screen. Denote:

$\xi =$ Survival probability in the general population

$RS(y) =$ Relative survival probability as a function of years since diagnosis

$r =$ Screening rate in general population

$RRR_M =$ Relative risk reduction of screening on disease-specific mortality

For the general population, we estimated life expectancy as the sum of conditional survival probabilities, plus one-half (assuming that, on average, an individual would die halfway between two ages): $LE_a = \frac{1}{2} + \sum_{a=a_0}^{\infty} \xi_{a|(a-1)}$. For individuals with disease, we estimated life expectancy as the sum-product of conditional survival probabilities for the general population multiplied by relative survival probabilities for individuals with colorectal cancer (described in the next section), plus one-half.

Relative survival probabilities. To estimate relative survival probabilities for individuals with colorectal cancer, we employed a weighted average of probabilities in the screening and no screening subgroups:

$$RS = r \cdot RS_s + (1 - r) \cdot RS_{ns}$$

The relative survival probability for individuals who did vs. did not receive screening varied by a relative risk reduction for mortality associated with screening (RRR_M), so that:

$$RS = r \cdot RS_s + (1 - r) \cdot (1 - RRR_M) \cdot RS_s$$

Table 1 in the main text shows parameter values, which were the same across disease stages. Using relative survival rates for the general population (colorectal cancer, all stages) from the Surveillance, Epidemiology, and End Results Program, we then derived relative survival probabilities for the population subgroups that received vs. did not receive colonoscopy, at annual intervals. For example, 10-year relative survival rate were 89.7% with colonoscopy and 31.4% absent screening (solved from 54.8% relative survival rate in the general population = 65.1% of the guideline-recommended population up-to-date with screening*61.7% of the up-to-date population obtained colonoscopy*[Relative survival rate with colonoscopy] + (1-65.1%*61.7%)*[Relative survival rate absent screening]*(1-65% relative risk reduction of colonoscopy on disease mortality). For flexible sigmoidoscopy and fecal occult blood testing, we interpolated subgroup relative survival probabilities as the relative risk reduction for each of those procedures as compared to colonoscopy, again at annual intervals.

Complications risk. Following previous literature, we modeled an increase in the probability of complications at patient age >65 years.[1] Specifically, that publication provided the 30-day observed rate of adverse events (serious gastrointestinal [perforations, bleeding, transfusions], other gastrointestinal [paralytic ileus, nausea and vomiting, dehydration, abdominal pain], and cardiovascular [MI or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, shock]) in Medicare beneficiaries ages 66-69, 70-74, 75-59, 80-84 and ≥85 years, adjusted for race, sex, urban vs. rural location, and socioeconomic status. We fit an exponential regression line the published rate of observed adverse events and applied the fitted value to a modeled patient's age.

Utility and risk aversion. To be willing to suffer the risk of fatal complications from disease screening, we assumed that an individual would require compensation in the form of increased life expectancy. Specifically, we assumed risk aversion, so that if an individual could achieve the same increase in life expectancy from two disease screening tests, one with less risk and another with more risk, they would prefer the test with less risk. This concept was distinct from discounting, which simply considers future life-years to be less valuable than the current life-year, without regard to risk.

As described in the main text, we considered a hypothetical individual who would require a proportionate increase in life expectancy to be willing to accept risk, and that this proportion would remain constant with age ("constant relative risk aversion"). Mathematically:

$$u(LE) = \frac{LE^{1-\alpha}}{1-\alpha}, \alpha \geq 0$$

Observe that when α=0, an individual is risk-neutral ($u(LE)$ is linear in life expectancy), and when α>0, an individual is risk-averse. In the scenarios presented in the main article, we considered individuals who were risk-neutral (alpha=0) or had varying degrees of risk aversion (moderate, alpha=3; or high, alpha=5). Parameters were based on estimates of risk aversion in the economics literature, which are often estimated as 2-3 and range up to 5.[2-7]

Required increase in life expectancy to accept potential risks of colonoscopy. As noted in the main article, risk-neutrality, moderate risk-aversion, and high risk-aversion corresponded to a 2-, 5-, and 8-month required increase in life expectancy to be willing to accept the potential risks of colonoscopy. These estimates were obtained by employing a parallel shift in survival curves from national life expectancy tables for a hypothetical 60-year-old individual. Denote:

DLE_{a_0} = Discounted life expectancy at age a_0

dLE_{a_0} = Change in life expectancy required to accept potential risks of colonoscopy at age a_0

with other notation as in earlier parts of this Supplement. We solved for dLE in the equation:

$$u\left(DLE_{a_0}\right) = (1-\kappa)\cdot u\left(DLE_{a_0} + dLE_{a_0}\right)$$

where

$$DLE_{a_0} = u\left(\underbrace{\sum_{a=a_0}^{\infty} \xi_{a|(a-1)} \frac{\overbrace{a-a_0}^{\text{survival years}}}{(1+DF)^a} + \frac{1}{2}}_{\text{discounted life expectancy}}\right)$$

and

$$DLE_{a_0} + dLE_{a_0} = u\left(\underbrace{\sum_{a=a_0}^{\infty} \xi_{a|(a-1)} \frac{\overbrace{a-a_0}^{\text{survival years}} + dLE}{(1+DF)^a} + \frac{1}{2}}_{\text{discounted life expectancy required to accept screening risks}}\right)$$

We assumed a_0=60 years, $DF = 3\%$ and $\kappa = 277/100{,}000$ (or higher for patients aged >65 years),[1] consistent with Table 1 of the main article.

Transfer to colonoscopy screening. To maintain consistency with clinical practice, a positive result on stool-based testing or flexible sigmoidoscopy prompted an individual to transfer to colonoscopy screening, at which time they could select a new screening frequency and age of cessation. As in the MISCAN (Microsimulation Screening Analysis) model utilized to inform the decision analysis accompanying USPSTF recommendations, the probability of a positive result was approximated by 1 minus the specificity of each method (Table 1).

Therefore, the life expectancy attributable to any non-colonoscopy screening strategy depended on both the life expectancy of the initial strategy plus that associated with backup strategies of colonoscopy, should the initial screening method yield a positive result. Table S1 illustrates the probability of various screening tests used to inform an initial strategy of stool-based testing testing.

Supplement References

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Supplement 2. Model validation

As described in the main text, the model was considered valid if it met the following 2 criteria for external validity and 4 criteria for internal validity:

External validity criteria #1: Model predictions for risk-neutral individuals—who, like national guidelines, weighed benefits and risks equally—were similar to USPSTF recommendations. PASSED: See the Results section of the main article and Table 2 for details.

External validity criteria #2: The magnitude of model-predicted increases in life expectancy were similar to predictions for life-years gained per 1000 individuals in the decision analysis accompanying USPSTF recommendations. PASSED: See Table S2 for details.

Internal validity criteria #1: The model predicted less intensive screening as risk-aversion increased (because an individual was more averse to potential complications). PASSED: See Table S3 for details.

Internal validity criteria #2: The model predicted less intensive screening as the discount rate increased (because preventing future cancer was less important). PASSED: See Table S4 for details.

Internal validity criteria #3: The model predicted less intensive screening for individuals with elevated risk of screening complications. PASSED: See the Results section of the main article and Table 3 for details.

Internal validity criteria #4: The model predicted more intensive screening for individuals with elevated risk of developing colorectal cancer. PASSED: See the Results section of the main article and Table 3 for details.

Table S1. Example of screening tests utilized to inform initial non-colonoscopy screening strategies

We illustrate screening tests utilized to inform an initial strategy of biennial stool-based testing between ages 50-74 years (total: 13 lifetime screenings), in a highly risk-averse individual.

Scenario	**Probability**	**Screening strategy**
No positive result on FOBT	1-(1-Specificity^13)	Stool-based testing 50-74 y, every 2 y
Positive result on Stool-based testing		
Age 50 y	1-Specificity	Transfer to colonoscopy 50-70y, every 20 y
Age 52 y	Specificity*(1-Specificity)	Transfer to colonoscopy 52-72y, every 20 y
Age 54 y	Specificity^2*(1-Specificity)	Transfer to colonoscopy 54-74y, every 20 y
Age 56 y	Specificity^3*(1-Specificity)	Transfer to colonoscopy 56-75y, every 19 y
Age 58 y	Specificity^4*(1-Specificity)	Transfer to colonoscopy 58-75y, every 17 y
Age 60 y	Specificity^5*(1-Specificity)	Transfer to colonoscopy 60-75y, every 15 y
Age 62 y	Specificity^6*(1-Specificity)	Transfer to colonoscopy 62-75y, every 13 y
Age 64 y	Specificity^7*(1-Specificity)	Transfer to colonoscopy 64-75y, every 11 y
Age 66 y	Specificity^8*(1-Specificity)	Transfer to colonoscopy 66-75y, every 9 y
Age 68 y	Specificity^9*(1-Specificity)	Transfer to one-time colonoscopy, 68 y
Age 70 y	Specificity^10*(1-Specificity)	Transfer to one-time colonoscopy, 70 y
Age 72 y	Specificity^11*(1-Specificity)	Transfer to one-time colonoscopy, 72 y
Age 74 y	Specificity^12*(1-Specificity)	Transfer to one-time colonoscopy, 74 y

Table S2. External validity criteria #2: Comparison of current model with other published models of colorectal cancer screening

"MISCAN" refers to Microsimulation Screening Analysis. "SimCRC" refers to Simulation Model of Colorectal Cancer. "CRC-SPIN" refers to Colorectal Cancer Simulated Population Model for Incidence and Natural History. See Appendix reference 8 for details.

Strategy	Ages	Frequency	Life-years gained per 1000 persons screened			
			Current Model*	MISCAN	SimCRC	CRC-SPIN
Colonoscopy	50-75 y	10 y	271	248	275	270
Flexible sigmoidoscopy with annual stool-based testing	50-75 y	10 y	266	246	270	256
Stool-based testing	50-75 y	1 y	234	231†	260†	244†

*Non-discounted life-years gained in a risk-neutral individual, multiplied by 1000 (to maintain comparability with assumptions of previously published models). †Shown for the 2016 USPSTF model-recommended stool-based testing strategy.

Table S3. Internal validity criteria #1

Inputs not specified follow Table 1 in the main article. *Flexible sigmoidoscopy with annual fecal occult blood testing.

Degree of relative risk aversion (α in Supplement 1)	**Most-preferred strategy**		
	Method*	**Ages (y)**	**Frequency (y)**
0	Colonoscopy	53-73	10
1	Colonoscopy	53-75	11
2	Colonoscopy	53-75	11
3	Flexible sigmoidoscopy	51-75	12
5	Flexible sigmoidoscopy	55-75	20
7	Flexible sigmoidoscopy	55-75	20
10	Flexible sigmoidoscopy	55-75	20

Table S4. Internal validity criteria #2

Inputs not specified follow Table 1 in the main article.

Degree of risk aversion	Discount rate	Most-preferred strategy		
		Method	Ages (y)	Frequency (y)
None (risk-neutral)	0%	Colonoscopy	51-75	12
	3%	Colonoscopy	53-73	10
Moderate	0%	Flexible sigmoidoscopy	51-75	12
	3%	Flexible sigmoidoscopy	51-75	12
High	0%	Flexible sigmoidoscopy	51-75	8
	3%	Flexible sigmoidoscopy	55-75	20