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# Should the Fecal Immunochemical Test (FIT) Threshold Vary by Sex?

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# Collaborators

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# Disclosures

- Indiana University receives support for TI's effort on projects in collaboration with Exact Sciences Corp



# What is known.....

- FIT – used most commonly for CRC screening
  - Measures fecal hemoglobin (f-hb) by immunoassay
- Test characteristics vary based on threshold
  - CRC sensitivity ~71% at  $> 20$  ug/g – ~78% at  $\leq 10$  ug/g
- CRC and advanced adenoma prevalence and distribution differ between males and females

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- ***Do the differences warrant different FIT thresholds?***



# Different FIT thresholds for males and females?

- Depends on

Goals - what matters most?

Outcomes - CRC incidence, CRC mortality, cost-effectiveness?

Which metric(s) to equalize – detection rate, PPV, sensitivity, specificity, other?

- One country currently using sex-specific thresholds
- What evidence?

70  $\mu\text{g/g}$  for men, 25  $\mu\text{g/g}$  for women – “narrowed the gap” in FIT positivity, and detection and PPV for CRC and AA\* - (but is this more “effective”?)

CEA of 181 FIT strategies – 25  $\mu\text{g/g}$  (males, 50-79) and 10  $\mu\text{g/g}$  (females, 55-69) annually† prevents 28% CRC cases and 55% CRC deaths at ICER of 9,000 € (\$9,720) / LY gained

\*Sarkeala T, et al. BMJ Open 2021;11:e046667

†Heinavaara S, et al. Preventive Medicine 2022;157:106990



# Study Aims

- Determine whether lesion-specific fecal hemoglobin (f-hb) levels differ in males and females
- Determine sex-specific sensitivity and specificity for
  - CRC
  - Advanced precancerous lesions (APLs = AAs + SSPs  $\geq$  1 cm)
- Identify factors associated with a positive FIT  
(What might explain sex-specific differences in test characteristics?)



# Methods

- Retrospective cross-sectional study (DeeP-C)
  - Pivotal study for current mt-sDNA
- FIT (and mt-sDNA) – colonoscopy as reference standard
  - OC-FIT-CHEK (Polymedco - Cortland, NY)
  - 100 ng/ml threshold (~ 20 ug/g feces)



# Methods

Comparison of f-hb between males and females based on the most advanced finding:

- Adenocarcinoma of the colon or rectum (CRC)
- Advanced precancerous lesion (APLs)
- Non-advanced neoplasia/SSPs < 1.0 cm
- Non-neoplastic finding
- “Clean colons” – no tissue taken





# Methods

- Sensitivity and specificity for
  - CRC
  - APLs.....at recommended threshold of 100 ng/ml ( $\sim 20 \mu\text{g/g}$ )
- Logistic regression
  - Demographic, clinical, endoscopic/histologic features associated with FIT sensitivity for CRC, APLs



# Results

- Study cohort N = 9,989
- Mean (SD) age = 62.4 (8.4) years
- 4,625 (46.3%) males
- 5,364 (53.7%) females
- CRCs = 65 (0.6%)
- APLs = 757 (7.6%)



# FIT hemoglobin levels by sex and most advanced findings (ng f-hb/mL buffer)

	Females			Males			P-value*
	N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)	
CRC	31	931 (1338)	<b>448 (11-1428)</b>	34	1151 (1515)	<b>1013 (125-1432)</b>	0.20
APLs	310	126 (379)	<b>0 (0-54)</b>	447	208 (600)	<b>9 (0-124)</b>	<b>&lt;0.001</b>
Non-advanced adenomas	1297	33 (174)	<b>0 (0-6)</b>	1596	55 (358)	<b>0 (0-13)</b>	<b>&lt;0.001</b>
Non-neoplastic findings	1061	28 (266)	<b>0(0-3)</b>	756	51 (405)	<b>0 (0-2)</b>	0.89
Clean colon	2665	24 (148)	<b>0 (0-1)</b>	1792	21 (136)	<b>0 (0-1)</b>	0.70



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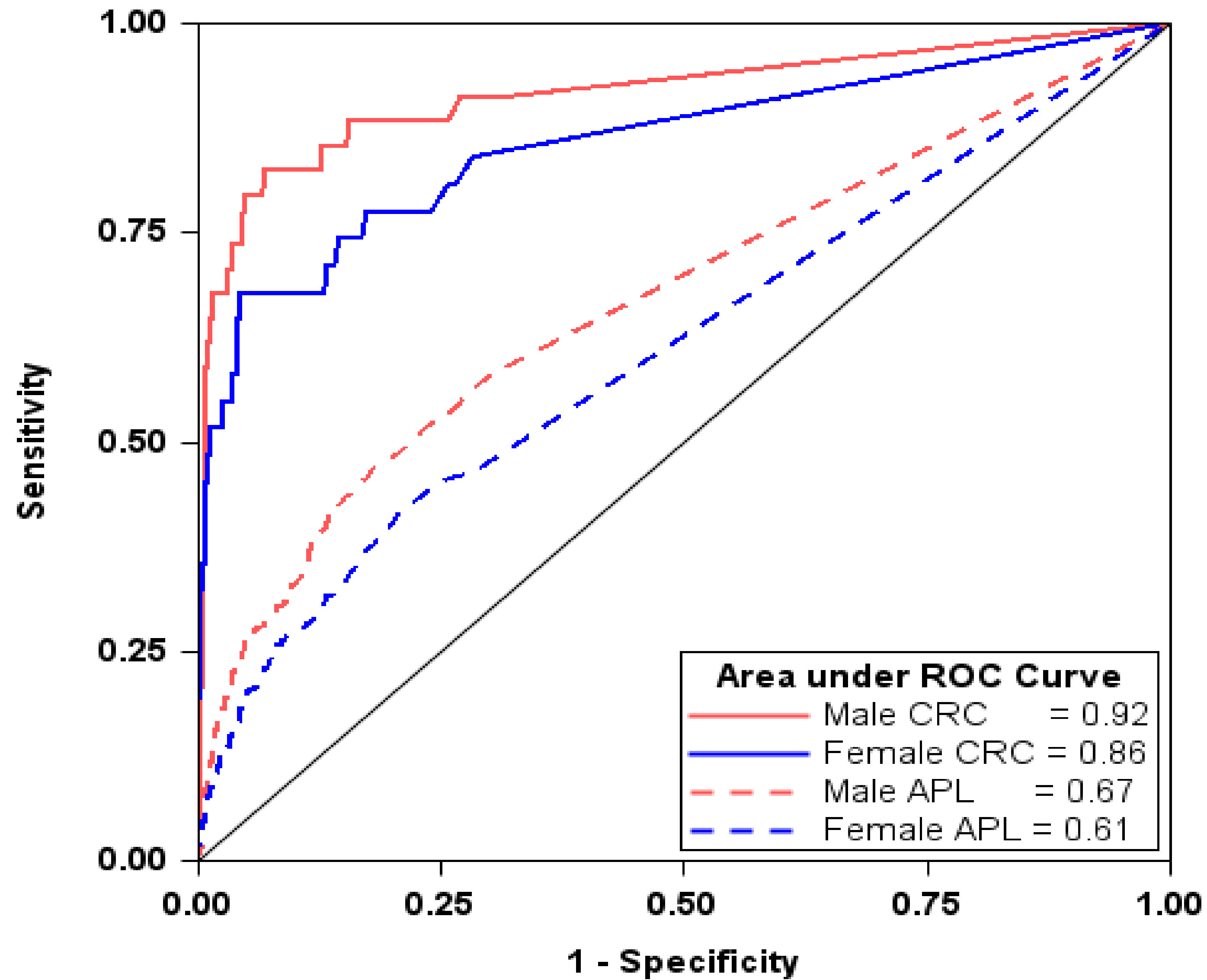
# Sex-specific FIT test characteristics (%) @ 100ng/ml

Parameter	Males	Females	P-value	Female threshold to = male sensitivity (& resulting specificity)
CRC (65) sensitivity	79.4 (62.1-91.3)	67.7 (48.6-83.3)	0.28	2 ng/ml (specificity=74.2%)
APL (757) sensitivity	26.8 (22.8-31.2)	19.4 (15.1-24.2)	0.02	40 ng/ml (specificity=89.6%)
Specificity*	94.5 (93.7-95.2)	95.2 (94.5-95.7)	0.14	At 95% specificity, male & female thresholds of 112 & 96 ng/ml, respectively

\*Includes non-advanced adenomas and no colorectal neoplasia groups



# Sex-specific AROC curves for CRC AND APLs



## Univariate - Distribution of CRC Size

<b>CRC Size</b>	<b>Females (n=31)</b>	<b>Males (n=34)</b>
< 5 mm	0	0
5 to 9 mm	4 (12.9)	1 (2.9)
10 to 19 mm	7 (22.6)	7 (20.6)
20 to 29 mm	4 (12.9)	8 (23.5)
≥ 30 mm	16 (51.6)	18 (52.9)
Mean (SD), mm	<b>29.8 (17.4)</b>	<b>32.6 (18.1)</b>
Median (IQR), mm	<b>30 (13-44)</b>	<b>30 (20-45)</b>



## Univariate - CRC Location

<b>CRC Location</b>	<b>Females</b>	<b>Males</b>
Proximal	19 (61.3)	11 (32.4)
Distal/Rectal	12 (38.7)	23 (67.6)
		<b>P = 0.002</b>





## CRC sensitivity\* by sex and location, % (95 CI)

<b>CRC Location</b>	<b>Females (n=31)</b>	<b>Males (n=34)</b>	<b>P-value</b>
Proximal	63.2 (38.4-83.7)	72.7 (39.0-94.0)	0.59
Distal/Rectal	75.0 (42.8-94.5)	82.6 (61.2-95.1)	0.84

\*At 100 ng/ml threshold



## Distribution of APL Size

APL size	N (%)	
	Females (n = 310)	Males (n = 447)
< 5 mm	3 (1%)	7 (1.6%)
5 to 9 mm	21 (7%)	5 (7.8%)
10 to 19 mm	239 (77%)	335 (75%)
20 to 29 mm	30 (9.7%)	49 (11%)
≥ 30 mm	17 (5.5%)	21 (4.7%)
Mean (SD), mm	<b>14.0 (6.5)</b>	<b>14.0 (6.5)</b>
Median (IQR), mm	<b>12 (10-15)</b>	<b>12 (10-15)</b>



## Distribution of APL subtype

APL subtype	N(%)	
	Females	Males
High-grade dysplasia	11 (3.5)	28 (6.3)
Villous histology	100 (32.5)	156 (34.9)
Tubular adenoma $\geq$ 1.0 cm	148 (47.7)	215 (48.1)
Serrated/HP $\geq$ 1.0 cm	51(16.5)	48 (10.7)

P=0.06



# Distribution of APL Location

APL Location	N (%)	
	Females	Males
Proximal	196 (63.2%)	235 (52.7%)
Distal/Rectal	114 (36.8%)	211 (47.3%)
		P= 0.004



## APL sensitivity\* by sex and location, % (95% CI)

<b>APL Location</b>	<b>Females</b>	<b>Males</b>	<b>P-value (M vs F)</b>
Proximal	13.3 (8.9-18.8)	17.4 (12.8-22.9)	0.23
Distal/Rectal	29.8 (21.6-39.1)	37.4 (30.9-44.4)	0.17
P-value (proximal vs. distal)	0.0004	< 0.0001	

\*At 100 ng/ml threshold



# Factors associated with OC-FIT-CHEK sensitivity for CRC

Variable	Value	Odds Ratio (95% CI)	P-value
<b>Sex</b>	<b><i>Female</i></b>	<i>Reference*</i>	<i>Reference</i>
	Male	1.33 (0.37 – 4.80)	0.66
<b>Smoking status</b>	<b><i>Never Smoked</i></b>	<i>Reference*</i>	<i>Reference</i>
	Current / Former Smoker	3.72 (0.98 – 14.17)	0.05
<b>Lesion size</b>	<b>&lt;30 mm</b>	Reference*	Reference
	≥30 mm	1.03 (0.29 – 3.69)	0.96
<b>Lesion location</b>	<b><i>Proximal</i></b>	<i>Reference*</i>	<i>Reference</i>
	Distal/Rectal	1.51 (0.42 – 5.40)	0.53
<b>CRC Stage</b>	<b><i>Stage I or Unstaged</i></b>	<i>Reference*</i>	<i>Reference</i>
	Stage II	1.46 (0.36 – 5.90)	0.60
	Stage III	3.92 (0.40 – 38.28)	0.24
	Stage IV	1.33 (0.10 – 16.88)	0.83

\*Category with lowest FIT sensitivity chosen as reference level for each factor



# Factors associated with OC-FIT-CHEK sensitivity for APLs

Variable	Value	Odds Ratio (95% CI)	P-value
Sex	<i>Female</i>	Reference	Reference
	Male	1.21 (0.83 – 1.78)	0.33
Smoking status	<i>Never Smoked</i>	Reference	Reference
	Current / Former Smoker	1.73 (1.18 – 2.53)	0.005
Lesion size	<10 mm	Reference	Reference
	10-19 mm	2.37 (1.08 – 5.17)	0.03
	20-29 mm	7.37 (3.07 – 17.71)	<0.0001
	≥30 mm	6.75 (2.50 – 18.18)	0.0002
Lesion location	<i>Proximal</i>	Reference	Reference
	Distal/Rectal	2.81 (1.93 – 4.08)	<0.0001
Lesion subcategory	<i>Serrated (SSL, HP) ≥ 10 mm</i>	Reference	Reference
	High grade dysplasia	11.30 (3.54 – 36.10)	<0.0001
	Villous adenoma	5.11 (1.92 – 13.59)	0.001
	Tubular adenoma ≥ 10 mm	5.63 (2.18 – 14.56)	0.0004



# Study Limitations

- Single brand FIT and single threshold
- Single study population
- Some male-female comparisons are underpowered
- No consideration of lesions other than the most advanced finding





# Conclusions

- For APLs and non-advanced neoplasia, males have higher f-hb levels than females
- No *statistically significant* difference in CRC sensitivity between males and females at 100 ng/ml
- APL sensitivity was higher in males and may be partially explained by a higher % of distal lesions
- Lesion size, location, smoking status, and advanced histology were independently associated with FIT sensitivity for APLs





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# Summary of selected studies of sex-specific FIT

1 <sup>st</sup> author, year, country	Study design	Main findings
Grobbee, 2016 Netherlands	FIT prior to screening colonoscopy in 1,256 (41% female)	More AN both detected and missed in males at all cutoffs. Sex-specific cutoffs could either = Se ( in females) or = missed lesions ( in males)
Selby, 2019, Switzerland & U.S.	Systematic review of 46 studies, 2.4 million participants; considered age, sex, FIT threshold on accuracy	In 3 studies (1.5 million participants) stratified by sex, pooled CRC sensitivity was 77% for males, 81% for females.
van Tourenhout 2014, Netherlands	3,022 who completed FIT prior to colonoscopy (any indication)	At all cutoffs, FIT sensitivity for CRC was higher and specificity lower for males. For AA, males had slightly higher sensitivity and lower specificity (NS)
Wilén, 2019 Sweden	1,182 with 1 or 2 +FITs at 10ug/g → colonoscopy	Lowering cutoff for females to equalize detection of AN would require 26-34% more colonoscopies.
Kortlever, 2021 Netherlands	1,112 average-risk, FIT prior to screening colonoscopy; LR model for risk of AN using age, sex, f-hb	Adding sex to the model did not improve model discrimination.



## Sensitivity (%) at f-hb cutoff set for 95% specificity (non-advanced adenomas and no neoplastic findings) for each sex

Sensitivity for:	Sex		P value
	Female 96 ng/mL cutoff	Male 112 ng/mL cutoff	
High Grade Dysplasia	45.5 (16.7-76.6) n=11	46.4 (27.5-66.1) n=28	0.96
Villous Lesions	22.0 (14.3-31.4) n=100	28.2 (21.3-36.0) n=156	0.16
Tubular adenomas /SSLs $\geq$ 20 mm	28.6 (11.3-52.2) n=21	50.0 (29.1-70.9) n=24	0.14
Any of the Above	25.0 (17.9-33.3) n=132	33.2 (26.8-40.0) n=208	0.07



# What do the modelers find?

- MISCAN-Colon Model – evaluated 181 FIT strategies, varying

Threshold – 10, 25, 40, 55, 70  $\mu\text{g/g}$

Interval – 1, 2, and 3 years

Starting age – 50, 55, 60, and 65 years

Stopping age – 69, 74, and 79 years

- .....versus no screening

	Start	Stop	Frequency	Threshold
Men	50 years	79 years	Annual	25 $\mu\text{g/g}$
Women	55 years	69 years	Annual	10 $\mu\text{g/g}$

- Prevents 28% CRC cases and 55% CRC deaths
- ICER of 9,000 £ (\$9,720) / LY gained

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