Colorectal cancer screening test accuracy

1. Clinical question/PICO

For persons without a CRC diagnosis or symptoms that might indicate CRC, which screening modality iFOBT, faecal or blood biomarkers, or any combination) performs best in detecting CRC, and how does the diagnostic performance change with family history, age, or sex?	
Population	Persons without a CRC diagnosis or symptoms that might indicate CRC (with a family history of CRC or no family history of CRC)
Intervention	Index Test 1: Screening for CRC with any of the following: • iFOBT • Faecal biomarkers • Blood-based biomarkers • Any combinations Index Test 2: An alternative screening test or no screening
Comparator	Colonoscopy findings or follow-up outcomes

2. Key findings

The results are summarised in Table A, Table B and Table C.

Table A. Summary of findings for diagnostic accuracy of iFOBT using a threshold of 10µg Haemoglobin/g faeces (iFOBT 10), iFOBT using a threshold of 20µg Haemoglobin/g faeces (iFOBT 20), multi-target stool DNA (mt-sDNA) and another stool DNA test (stool DNA test)

Outcome	***Studies (Participants)***	***Certainty of the evidence (GRADE)***	***Summary sensitivity (%, 95% CI)***	***Summary specificity (%, 95% CI)***	***Implications in Australian populations undergoing screening* with outcome prevalences of those aged***				
					40 years[a]	***45 years[b]***	***50 years[c]***	***74 years[d]***	***80 years[e]***
iFOBT 10									
Colorectal cancer (CRC)	4 (6510)	Very low[1]	92 (74–98)	88 (86–90)	Of 17 participants with CRC, 1 will be missed. Of those without CRC, 1198 will be offered colonoscopy.	Of 24 participants with CRC, 2 will be missed. Of those without CRC, 1197 will be offered colonoscopy.	Of 34 participants with CRC, 3 will be missed. Of those without CRC, 1196 will be offered colonoscopy.	Of 137 participants with CRC, 11 will be missed. Of those without CRC, 1184 will be offered colonoscopy.	Of 328 participants with CRC, 26 will be missed. Of those without CRC, 1161 will be offered colonoscopy.
Advanced adenoma (AA)	3 (10364)	Low[2]	38 (30–47)	91 (88–93)	Of 99 participants with AA 61 will be missed. Of those without AA, 891 will be offered a colonoscopy.	Of 189 participants with AA 117 will be missed. Of those without AA, 883 will be offered a colonoscopy.	Of 328 participants with AA 203 will be missed. Of those without AA, 870 will be offered a colonoscopy.	Of 1137 participants with AA 705 will be missed. Of those without AA, 798 will be offered a colonoscopy.	Of 1979 participants with AA 1227 will be missed. Of those without AA, 722 will be offered a colonoscopy.

Serrated lesion (SL)**	1 (6198)	Low[3]	12.4 (6.3–21.0)	89.6 (88.8–90.4)	Of 863 participants with SL 756 will be missed.	Of 824 participants with SL 722 will be missed	Of 766 participants with SL 671 will be missed	Of 718 participants with SL 629 will be missed	Of 857 participants with SL 751 will be missed
Advanced serrated lesion	2 (7113)	Very low[4]	14 (8–24)	90 (89–91)	Not calculable^				
Advanced precancerous lesion	1 (805)	Low[5]	25.0 (16.0–35.9)	88.8 (86.3–91.0)	Not calculable^				
iFOBT 20									
Colorectal cancer (CRC)	11 (1082528)	Moderate[6]	84 (82–86)	95 (94–96)	Of 17 participants with CRC, 3 will be missed. Of those without CRC, 499 will be offered colonoscopy.	Of 24 participants with CRC, 4 will be missed. Of those without CRC, 499 will be offered colonoscopy.	Of 34 participants with CRC, 5 will be missed. Of those without CRC, 498 will be offered colonoscopy.	Of 137 participants with CRC, 22 will be missed. Of those without CRC, 493 will be offered colonoscopy.	Of 328 participants with CRC, 52 will be missed. Of those without CRC, 484 will be offered colonoscopy.
Advanced adenoma (AA)	4 (11773)	Low[2]	24 (18–32)	96 (95–96)	Of 99 participants with AA 75 will be missed. Of those without AA, 396 will be offered a colonoscopy.	Of 189 participants with AA 144 will be missed. Of those without AA, 392 will be offered a colonoscopy.	Of 328 participants with AA 249 will be missed. Of those without AA, 387 will be offered a colonoscopy.	Of 1137 participants with AA 864 will be missed. Of those without AA, 355 will be offered a colonoscopy.	Of 1979 participants with AA 1504 will be missed. Of those without AA, 321 will be offered a colonoscopy.
Serrated lesion (SL)**	3 (8556)	Low[2]	5 (3–9)	95 (94–97)	Of 863 participants with SL 820 will be missed.	Of 824 participants with SL 783 will be missed	Of 766 participants with SL 728 will be missed	Of 718 participants with SL 682 will be missed	Of 857 participants with SL 814 will be missed
Advanced serrated lesion	3 (9030)	Very low[7]	8 (4–15)	96 (95–97)	Not calculable^				
Advanced precancerous lesion	2 (4995)	Low[2]	19 (16–23)	95 (95–96)	Not calculable^				
Mt-sDNA + haemoglobin test									
Colorectal cancer (CRC)	1 (2240) *Score 165*	Very low[1]	90.5 (77.4–97.3)	88.5 (87.1–89.8)	Of 17 participants with CRC, 2 will be missed. Of those without CRC, 1148 will be offered colonoscopy.	Of 24 participants with CRC, 2 will be missed. Of those without CRC, 1147 will be offered colonoscopy.	Of 34 participants with CRC, 3 will be missed. Of those without CRC, 1146 will be offered colonoscopy.	Of 137 participants with CRC, 13 will be missed. Of those without CRC, 1134 will be offered colonoscopy.	Of 328 participants with CRC, 31 will be missed. Of those without CRC, 1112 will be offered colonoscopy.
	1 (1014) *Score 183*		85.7 (42.1–99.6)	84.9 (82.5–87.1)	Of 17 participants with CRC, 2 will be missed. Of those without CRC, 1507 will be	Of 24 participants with CRC, 3 will be missed. Of those without CRC, 1506 will be	Of 34 participants with CRC, 5 will be missed. Of those without CRC, 1505 will be	Of 137 participants with CRC, 20 will be missed. Of those without CRC, 1489 will be	Of 328 participants with CRC, 47 will be missed. Of those without CRC, 1460 will be

					offered colonoscopy.	offered colonoscopy.	offered colonoscopy.	offered colonoscopy.	offered colonoscopy.
Advanced adenoma (AA)	1 (980) *Score 183*	Very low[8]	47.8 (37.3–58.5)	89.1 (86.8–91.1)	Of 99 participants with AA 52 will be missed. Of those without AA, 1079 will be offered a colonoscopy.	Of 189 participants with AA 99 will be missed. Of those without AA, 1069 will be offered a colonoscopy.	Of 328 participants with AA 171 will be missed. Of those without AA, 1054 will be offered a colonoscopy.	Of 1137 participants with AA 594 will be missed. Of those without AA, 966 will be offered a colonoscopy.	Of 1979 participants with AA 1033 will be missed. Of those without AA, 874 will be offered a colonoscopy.
Serrated lesion	NR								
Advanced serrated lesion	1 (1917) *Score 165*	Very low[4]	9.5 (1.2–30.4)	91.0 (89.7–92.3)	Not calculable^				
	1 (915) *Score 183*		40.7 (22.4–61.2)	89.1 (86.8–91.1)	Not calculable^				
Advanced precancerous lesion	1 (2198) *Score 165*	Very low[9]	27.2 (22.2–32.5)	91.0 (89.7–92.3)	Not calculable^				
	1 (816) *Score 183*		32.7 (19.9–47.5)	95.2 (93.4–96.6)	Not calculable^				
Stool 2 gene DNA test									
Colorectal cancer (CRC)	1 (2240) *Score 297*	Moderate[10]	92.9 (80.5–98.5)	88.1 (86.7–89.4)	Of 17 participants with CRC, 1 will be missed. Of those without CRC, 1188 will be offered colonoscopy.	Of 24 participants with CRC, 2 will be missed. Of those without CRC, 1187 will be offered colonoscopy.	Of 34 participants with CRC, 2 will be missed. Of those without CRC, 1186 will be offered colonoscopy.	Of 137 participants with CRC, 10 will be missed. Of those without CRC, 1174 will be offered colonoscopy.	Of 328 participants with CRC, 23 will be missed. Of those without CRC, 1151 will be offered colonoscopy.
Advanced adenoma (AA)	NR								
Serrated lesion (SL)	NR								
Advanced serrated lesion	1 (1917) *Score 297*	Very low[7]	14.3 (3.0–36.3)	91.8 (90.5–93.0)	Not calculable^				
Advanced precancerous lesion	1 (2198) *Score 297*	Low[2]	35.1 (29.7–40.8)	91.8 (90.5–93.0)	Not calculable^				

CI = confidence interval; iFOBT = immunochemical faecal occult blood test; NR = not reported

** N = 10,000 and assuming 100% underwent screening*

*** Implications based on based on specificity ie numbers with serrated lesion offered colonoscopy not calculated as sensitivity so low*

^ do not have prevalence estimates of advanced serrated lesions or advanced precancerous lesions for Australian populations

[1] High or unclear risk of bias due to loss to follow-up; imprecision as < 100 events; publication bias likely

[2] Unclear risk of bias due to loss to follow-up; imprecision as sensitivity estimates < 50%

[3] Unclear risk of bias due to loss to follow-up; imprecision as < 100 events

[4] Unclear risk of bias due to loss to follow-up; indirectness as analysis population of at least 50% of studies excluded advanced adenomas as well as CRCs; imprecision as < 100 events; publication bias likely

[5] Imprecision as < 100 events; publication bias likely

[6] High or unclear risk of bias due to loss to follow-up

[7] Unclear risk of bias due to loss to follow-up; indirectness as analysis population of at least 50% of studies excluded advanced adenomas as well as CRCs; imprecision as < 100 events

[8] Unclear risk of bias due to loss to follow-up; imprecision as < 100 events; publication bias likely

[9] Unclear risk of bias due to loss to follow-up; imprecision as sensitivity estimates < 50%; publication bias likely

[10] Imprecision as < 100 events

[a] Estimated prevalence in Australian unscreened population of aged 40 years in 2019; CRC 1.7/1000; AA 9.9/1000; sessile serrated lesions 86.3/1000

[b] Estimated prevalence in Australian unscreened population of aged 45 years in 2019; CRC 2.4/1000; AA 18.9/1000; sessile serrated lesions 82.4/1000

[c] Estimated prevalence in Australian eligible screening population of aged 50 years in 2019; CRC 3.4/1000; AA 32.8/1000; sessile serrated lesions 76.6/1000

[d] Estimated prevalence in Australian eligible screening population of aged 74 years in 2019; CRC 13.7/1000; AA 113.7/1000; sessile serrated lesions 71.8/1000

[e] Estimated prevalence in Australian eligible screening population of aged 80 years in 2019; CRC 32.8/1000; AA 197.9/1000; sessile serrated lesions 85.7/1000

Table B. Summary of findings for diagnostic accuracy for the detection of colorectal cancer by iFOBT using a threshold of 20µg Haemoglobin/g faeces (IFOBT 20) by sex, age and screen

Outcome	***Sex***	***Age***	***Screen***	***Studies (Participants)***	***Certainty of the evidence (GRADE)***	***Sensitivity (%, 95% CI)***	***Specificity (%, 95% CI)***
iFOBT 20							
Colorectal cancer	**Male**	50–74 years	NR	1 (245520)	Moderate[1]	86.4 (84.5–88.1)	92.4 (92.3–92.5)
	Female	50–74 years	NR	1 (286308)	Moderate[1]	75.8 (73.2–78.4)	94.8 (94.7–94.9)
	Male	**< 50 years**	NR	1 (15218)	Low[2]	75.0 (19.4–99.4)	97.2 (97.0–97.5)
	Male	**≥ 50 years**	NR	1 (2018)	Low[2]	87.5 (47.3–99.7)	95.5 (94.5–96.3)
	Male + female	50–70 years	**First**	1 (319425)	Moderate[1]	84.5 (81.5–87.2)	96.4 (96.3–96.4)
	Male + female	50–70 years	**Second**	1 (182592)	Moderate[1]	75.4 (68.7–81.3)	96.9 (96.8–97.0)

CI = confidence interval; iFOBT = immunochemical faecal occult blood test; NR = not reported
[1] High or unclear risk of bias due to loss to follow-up
[2] High or unclear risk of bias due to loss to follow-up; imprecision as < 100 CRCs

Table C. Summary of findings for studies comparing diagnostic accuracy for the detection of colorectal cancer by different tests in the same population

Outcome (events)	***Study (Participants)***	***Certainty of the evidence (GRADE)***	***Index test***	***Sensitivity (%, 95% CI)***	***Specificity (%, 95% CI)***
iFOBT 10 vs iFOBT 20 vs mt-sDNA + haemoglobin test					
Colorectal cancer (7)	Bosch 2019 (1014)	Very low[1]	iFOBT 10	100 (59.0–100)	90.9 (88.9–92.6)
			iFOBT 20	85.7 (42.1--99.6)	94.8 (93.3–96.1)
			mt-sDNA score 183	85.7 (42.1–99.6)	84.9 (82.5–87.1)
iFOBT 20 vs mt-sDNA + haemoglobin test vs stool 2 gene DNA					
Colorectal cancer (42)	Jin 2022 (2240)	Moderate[2]	iFOBT 20	81.0 (65.9–91.4)	94.7 (93.7–95.6)
			mt-sDNA score 165	90.5 (77.4–97.3)	88.5 (87.1–89.8)
			Stool DNA test 2	92.9 (80.5–98.5)	88.1 (86.7–89.4)

CI = confidence interval; iFOBT = immunochemical faecal occult blood test; iFOBT 10 = iFOBT with threshold of 10µg Haemoglobin/g faeces; iFOBT 20 = iFOBT with threshold of 20µg Haemoglobin/g faeces; mt-sDNA = multi-target stool DNA; NR = not reported
[1] Unclear risk of bias due to loss to follow-up; imprecision as < 100 events; Publication bias likely
[2] Imprecision as < 100 CRCs

Evidence sources

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