Systematic review report for question PSC1b

Clinical Question PSC1: *Is population screening based on testing with (a) immunochemical FOBT (iFOBT), (b) flexible sigmoidoscopy, (c) colonoscopy, (d) faecal biomarkers such as DNA (e) plasma biomarkers such as DNA (f) any combination of the above screening tests effective in reducing bowel cancer mortality rates, feasible, acceptable and a cost-effective method of screening for the target population?*
a) Is population screening starting at an earlier age more effective, feasible, acceptable and cost-effective, compared with starting at age 50 yr?
b) In population screening, do the harms outweigh the benefits if routine screening by any method is continued beyond the age of 75yr?

PICO PSC1b: *For persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical faecal occult blood test [iFOBT], flexible sigmoidoscopy, colonoscopy, faecal or blood biomarkers, or any combination) performs best in detecting colorectal cancer, and how does the diagnostic performance change with family history, age, or sex?*

Population	Index Test 1	Index Test 2	Reference standard	Outcomes
Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer (with a family history of colorectal cancer or no family history of colorectal cancer)	Screening for CRC with: - Immunochemical FOBT, or - Flexible sigmoidoscopy, or - Colonoscopy, or - Faecal biomarkers, or - Blood biomarkers, or - Any combinations	An alternative screening test or no screening	Colonoscopy or long-term follow up	Diagnostic performance related to advanced adenoma and colorectal cancer

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature Search

PubMed (01/01/2007-31/08/2016), Embase (01/01/2007-31/08/2016), CINAHL (01/01/2004-31/08/2016), PsycINFO (01/01/2004-31/08/2016), Cochrane Database of Systematic Reviews (01/01/2004-31/08/2016), Database of Abstracts of Reviews of Effects and Health Technology Assessment databases (up to 31/08/2016) were searched using text terms and, where available, database specific subject headings. Each database was

searched for articles dealing with colorectal cancer. In PubMed, Embase, CINAHL and PsycINFO databases the colorectal cancer search was coupled with a search for screening, and database specific filters for publication type/publication time and language. To identify studies which considered Aboriginal and Torres Strait Islanders (ATSI) these searches were then coupled with search terms for ATSI. A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all relevant articles were checked for potential additional articles.

1.3. Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic accuracy	
Study design	- Systematic reviews of Level II evidence, randomised controlled trials, or - Fully paired diagnostic study, or paired randomised cohort study.	Diagnostic case-control studies or studies of diagnostic yield
Population	Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer (with a family history of colorectal cancer or no family history of colorectal cancer)	
Index Test 1	Screening test for colorectal cancer: - Immunochemical FOBT, or - Flexible sigmoidoscopy, or - Colonoscopy, or - Faecal biomarkers, or - Blood biomarkers, or - Any combinations.	
Index Test 2	An alternative screening test or no screening.	
Reference standard	Colonoscopy or long-term follow up	
Outcomes	- Advanced adenoma detection rate, or - Colorectal cancer detection rate, or - Sensitivity and/or specificity for advanced adenomas, or - Sensitivity and/or specificity for colorectal cancers - Subgroup analysis of above outcomes for family history, age, gender	
Language	English	
Publication period	01/01/2007 to 31/08/2016	

2. Results

2.1. Search for relevant guidelines

Nine potentially relevant guidelines were identified and are detailed in Appendix C. Six however were not included as they did not meet the pre-specified criteria. Three guidelines were identified which potentially could address this clinical question. These were:

1. *Ontario HTA Series 2009, FOBT for Colorectal Cancer Screening An Evidence-Based Analysis.*
2. *International Agency for Research on Cancer 2010, European guidelines for quality assurance in colorectal cancer screening and diagnosis.*
3. *US Preventive Services Task Force, Screening for Colorectal Cancer 2016.*

As both these guidelines contained substantial publications which did not met the inclusion criteria described above, thus we only included literature that met the inclusion described above. As for the 2016 US PSTF Colorectal Cancer Screening guideline, this was published during the prepared of this review, and thus contains the same literature described here. These 2 guidelines were used to source literature up to 2009, with a 2 year overlap (2007-2009) with the literature search described in this systematic review.

2.3 Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The combined PubMed and Embase searches identified 13262 citations, the Cochrane Database of Systematic Reviews search identified 12 citations, the Database of Abstracts of Reviews of Effects (DARE) search identified 25 citations, the Health Technology Assessment search identified 27 citations, PsycINFO search identified 333 citations, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) search identified an additional 344 citations, resulting in a total of 14003 citations. Titles and abstracts were examined and 188 articles were retrieved for a more detailed evaluation.

A total of 29 diagnostic accuracy studies were reported in 29 articles met the inclusion criteria and were included in the review. There were no studies of ATSI people that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they had used an inappropriate study design, or included inappropriate participants.

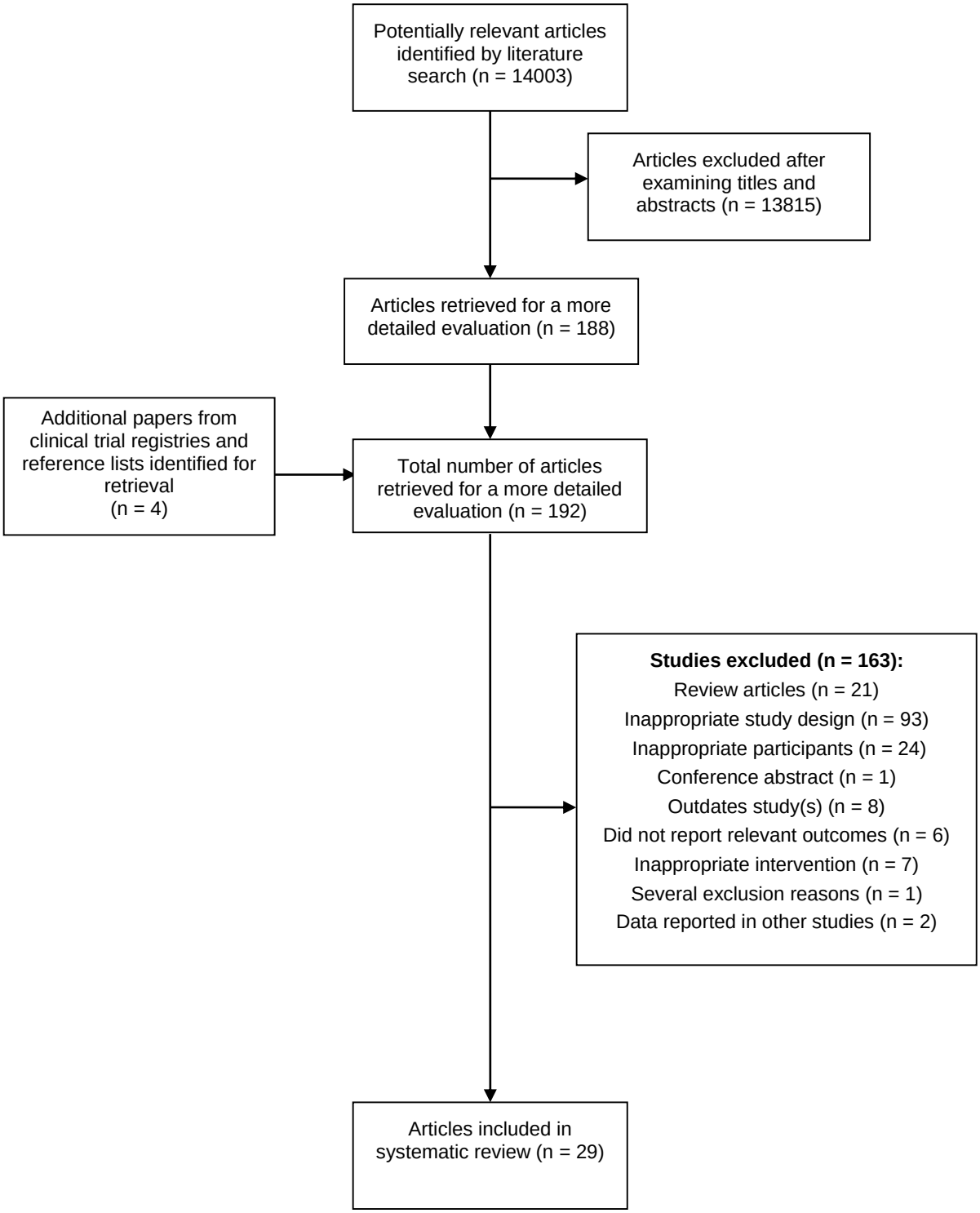

Figure 1. Process of inclusion and exclusion of studies

2.4 Study Characteristics

Characteristics of included studies are described in Tables 1 - 9.

Table 1: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Ahlquist 2008 (USA)	Multicenter, prospective, triple-blinded trial, targeting average-risk persons, from 2001 to 2007. Recruited asymptomatic persons age 50 to 80 years who were at average risk for colorectal cancer from communities surrounding 22 participating academic and regional health care systems through direct mail and multi-media advertisements. **N = 3764**	Diagnostic accuracy	Stool DNA Test 1 (Tumor specific point mutations (K-ras, APC, & p53), BAT-26; and long DNA) **N = 2497** Stool DNA Test 2 (K-ras mutations, APC mutator cluster regions, and methylation of the vimentin) **N = 217**	Colonoscopy	Positivity Sensitivity Specificity PPV NPV
Annahazi 2016 (Hungry)	Patients referred to our specialist colorectal unit in the First Department of Medicine, Szeged, Hungary were enrolled in the study, who all underwent colonoscopy. **Men/Women:** 53.2%/46.8% **Age range:** 29–91 years **Age mean:** 66.0 years **N = 109**	Diagnostic accuracy	Faecal MMP-9 protein levels (human 92 kDa Pro-MMP-9 and 82 kDa active form of MMP-9) (Abingdon, UK)	Colonoscopy	Sensitivity Specificity AUC
Brenner 2010 (Germany) BLITZ study	Participants of the German screening colonoscopy program were recruited in gastroenterology practices in Southern Germany **Age (mean):** Men: 63.0 years Women: 62.0 years **Men/Women:** 49.8%/50.2% **N = 2,324**	Diagnostic accuracy	6 iFOBTs: - Bionexia FOBplus (DIMA) - PreventID CC (Preventis) - immoCARE-C (CAREdiagnostica) - FOB advanced (Ultimed) - QuickVue iFOB (Quidel) - Bionexia Hb/Hp Complex (DIMA)	Colonoscopy	Sensitivity, specificity, PPV, NPV for detection of advanced neoplasms

N = number of participants; USA = United States of America; BLITZ = Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfru¨herkennung; UK = United Kingdom; iFOBT = immunochemical faecal occult blood test; DNA = deoxyribonucleic acid; kDa = kilodaltons; PPV = positive predictive value; NPV = negative predictive value

Table 2: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Brenner 2013 (Germany) BLiTz study	Participants of the German screening colonoscopy program were recruited in gastroenterology practices in Southern Germany and invited to provide blood and stool samples for evaluation of novel CRC screening tests. **Age mean:** 62.7 years **Men/Women:** 49.2%/50.8% **N = 2,235**	Diagnostic accuracy	3 iFOBTs: RIDASCREEN Haemoglobin, RIDASCREEN Haemo-Haptoglobin Complex (R-Biopharm AG, Darmstadt, Germany) OC SENSOR	Colonoscopy	Sensitivity, specificity, PPV, NPV, PLR, and NLR for detecting CRC, any advanced neoplasm
Castro 2014 (Spain)	Study population consisted of asymptomatic individuals with at least one FDR with histologically confirmed CRC consecutively referred to perform a colonoscopy as a CRC screening method. **Age mean(SD):** 54.83±10.49 years **Men/Women:** 41.2%/58.8% **N = 595**	Diagnostic accuracy with family history	FIT + FITmax OCsensor^{TM} (Eiken Chemical)	Colonoscopy	sensitivity, specificity, PPV, NPV, PLR, Youden index
Chen 2014 (Adv Dig Med) (Taiwan)	Asymptomatic population that underwent a health examination at the Health Care Center of Chang Gung Memorial Hospital (Guieshan, Taiwan). Non-hospitalized persons were consecutively enrolled between January 2008 and June 2009. **Age mean(SD):** 53.65±8.42 years **Men/Women:** 56.1%/43.9% **N = 6096**	Diagnostic accuracy	iFOBT OC-LIGHT system (Eiken Chemical)	Colonoscopy	sensitivity, specificity, PPV, NPV,

N = number of participants; USA = United States of America; BLiTz = Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfru¨herkennung; FDR = first degree relative; SD = standard deviation; CRC = colorectal cancer; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; DNA = deoxyribonucleic acid; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio

Table 3: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Chiu 2013 (Taiwan) PRESEPT study	Prospectively enrolled consecutive asymptomatic adult individuals who underwent screening colonoscopy as part of thorough health check-ups at the Health Management Center of National Taiwan University Hospital between September 2005 and September 2010. **Men/Women:** 59.2%/40.8 **Age mean(SD):** 59.8±7.6 years **N = 18,296**	Diagnostic accuracy	iFOBT (OC-LIGHT; Eiken Chemical, Tokyo, Japan)	Colonoscopy	sensitivity, specificity, PPV, NPV, Number needed to scope
Church 2014 (USA + Germany)	Subjects at least 50 years old and scheduled for colonoscopy at one of the participating clinical centres were approached about volunteering for the study. To ensure that only average risk individuals were enrolled, we excluded those with previous lower endoscopy, previous CRC or adenomas; iron deficiency anaemia or haematochezia (blood in the stool) within the previous 6 months; or family history indicating increased risk for the disease (two or more first degree relatives with CRC or one or more with CRC at age 50 years or less; or known Lynch syndrome or familial adenomatous polyposis). **N = 6,874**	Diagnostic accuracy	Plasma methylated SEPT9 DNA (Epi proColon Assay)	Colonoscopy	**Primary** *Sensitivity, specificity and PPV, NPV for CRC.* **Secondary** *Sensitivity for AA and for NA, and to accrue as many HGD as possible.*
De Wijkerslooth 2012 (Netherlands) COCOS-trial	Between June 2009 and July 2010, a total of 6,600 asymptomatic individuals of the Amsterdam and Rotterdam regions were randomly selected from the regional municipal administration registrations and invited for colonoscopy screening. The protocol of this population-based screening pilot (COCOS-trial). **Age median(IQR):** 60(55-65) years **Men/Women:** 51%/49% **N = 1,256**	Diagnostic accuracy	iFOBT (OCSensor, Eiken Chemical, Tokyo, Japan)	Colonoscopy	Sensitivity, specificity, PLR, NLR, AUC of ROC

N = number of participants; USA = United States of America; SD = standard deviation; CRC = colorectal cancer; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; DNA = deoxyribonucleic acid; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio; AA = advanced adenoma; NA = non-advanced adenoma; HGD = high grade dysplasia; AUC = area under the curve; ROC = receiver operating characteristic

Table 4: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Elsafi 2015 (Saudi Arabia)	Prospective cohort study protocol, including patients who reported to two tertiary hospitals in the eastern region of Saudi Arabia – King Fahd Military Medical Complex (Dhahran, Saudi Arabia); and King Faisal Specialist Hospital (Dammam, Saudi Arabia) from June 2012 through May 2013. All asymptomatic participants that reported to hospital in this study were 50–74 years of age. **Age mean(SD):** 63.8(7.9) years **Men/Women:** 68.2%/31.8% **N = 277**	Diagnostic accuracy	iFOBT: RAPEPKT313 kit (DIAsource, Belgium)	Colonoscopy	Sensitivity, specificity, PLR, NLR, PPV, NPV.
Gimeno-Garcia 2009 (Spain)	From November 2005 to December 2006, 3693 individuals aged 50-79 years among 71 673 inhabitants in the Northern area of Tenerife, were randomly selected from the Social Security Register of the Government of the Canary Islands (Spain). They were contacted by telephone and invited to participate in a CRC screening program using FOBT. Nine hundred and six first-degree relatives of 159 patients with sporadic CRC were registered. Among them, 210 familiars (parents and siblings) were contacted and they agreed to participate in the study. **Age mean(SD):** 57 (9.5) years **Men/Women:** 30.2%/69.8% **N = 116**	Diagnostic accuracy with family history	iFOBT OC-Light (Eiken Chemical Co., Tokyo, Japan)	Colonoscopy	sensitivity, specificity, PPV, NPV,
Hernandez 2014 (Spain) COLONPREV study	A multicentre, prospective, blinded, cohort study of diagnostic test was performed in three tertiary hospitals in Spain between 1/01/2010 and 30/06/2011. Asymptomatic men and women aged 50 to 69 years, included in the COLONPREV study in Galicia and Euskadi were invited to participate in this diagnostic test study if they were offered a colonoscopy during the inclusion period. **Age mean(SD):** 57.55 (4.55) years **Men/Women:** 49.6%/50.4% **N = 779**	Diagnostic accuracy	FIT1 and FITmax OC-sensor™ (Eiken Chemical Co, Tokyo, Japan)	Colonoscopy	Sensitivity, specificity, PPV, NPV, as well as PLR and NLR for the best cut-off

N = number of participants; SD = standard deviation; CRC = colorectal cancer; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio

Table 5: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Hundt 2009 (Germany) BliTz study	The analyses were part of the BliTz study, an ongoing screening study conducted in cooperation with 20 gastroenterology practices in southwestern Germany since January 2006. The study includes participants undergoing screening colonoscopy a procedure that the German health care system has offered since October 2002 to average-risk persons ≥55 years. **Age mean:** **Men:** 63.5 years **Women:** 62.4 years **Men/Women:** 50.4%/49.6% **N = 1319**	Diagnostic accuracy	6 iFOBTs: Bionexia FOBplus (DIMA) Bionexia Hb/Hp Complex (DIMA) PreventID CC (Preventis) immoCARE-C (CAREdiagnostica) FOB advanced (Ultimed) QuickVue iFOB (Quidel)	Colonoscopy	Sensitivity, specificity, PPV, NPV, PLR, NLP
Imperiale 2014 (USA)	The target population was asymptomatic persons between the ages of 50 and 84 years who were considered to be at average risk for colorectal cancer and who were scheduled to undergo screening colonoscopy. Enrollment was weighted toward persons 65 years of age or older in order to increase the prevalence of cancer. **Age mean(SD):** 64.2(8.41) years **Men/Women:** 46.3%/53.7% **N = 9989**	Diagnostic accuracy	The multitarget stool DNA test consists of molecular assays for aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS,* and β-actin (a reference gene for human DNA quantity), iFOBT (OC FIT-CHEK, Polymedco)	Colonoscopy	Specificity, sensitivity, AUC

N = number of participants; BLITZ = Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfru¨herkennung; USA = United States of America; SD = standard deviation; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; DNA = deoxyribonucleic acid; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio; AUC = area under the curve

Table 6: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Kato 2009 (Japan)	Potentially eligible subjects were participants in a comprehensive health program at Kameda General Hospital or Kameda Makuhari Clinic between April 1983 and March 2002. We consecutively enrolled 22,666 persons who had undergone colonoscopy and iFOBT. All eligible subjects were asymptomatic and participated voluntarily in this program. **Age mean(SD):** 48.2(9.3) years **Men/Women:** 72.0%/28.0% **N = 21,794**	Diagnostic accuracy	iFOBT (Fujirebio Inc, Tokyo, Japan)	Colonoscopy	Sensitivity, Specificity
Lee 2013 (Taiwan)	First, beginning on 1 March 2011, we recruited participants at the National Taiwan University Hospital (Health Management Center; Taipei, Northern Taiwan) through advertising messages for cancer screening. Participants >18 years of age who had completed the IFOBT, guaiac based test, HPSA and bidirectional endoscopy were included. **Age mean(SD):** 53.0(11.7) years **Men/Women:** 60.5%/39.5% **N = 3172**	Diagnostic accuracy	iFOBT (OC-SENSOR; Eiken Chemical, Tokyo, Japan)	Colonoscopy	Sensitivity, Specificity, PLR, NLR
Levy 2014 (USA)	Individuals aged 40 to 75 who were scheduled for a screening, surveillance or diagnostic colonoscopy at University of Iowa Healthcare were mailed an invitation to participate in the study. Only the screening group included in this review. **Age mean(SD):** 56.9 (7.6) years **Men/Women:** 40.8%/59.2% **N = 621 (Screening group only)**	Diagnostic accuracy	4x iFOBTs Inverness Clearview ULTRA iFOB Alere Clearview iFOB Complete Polymedco OC-Light iFOB Quidel QuickVue iFOB	Colonoscopy	Sensitivity, Specificity, PPV, NPV, PLR, NLR

N = number of participants; USA = United States of America; HPSA = Helicobacter pylori stool antigen test; SD = standard deviation; CRC = colorectal cancer; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio

Table 7: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Khalid-de Bakker 2011 (Netherlands)	Employees of the Maastricht University Medical Center, aged 50 to 65 years, were invited to participate in a CRC screening trial using primary colonoscopy. Exclusion criteria were severe comorbidity, colonoscopy within the previous 5 years, surveillance after polypectomy or CRC, and development of lower gastrointestinal symptoms in the 3 months prior to colonoscopy. **Age mean(SD):** 54.6 (3.7) years **Men/Women:** 41.6%/58.4% **N = 329**	Diagnostic accuracy	iFOBT OC-sensor test (Eiken Chemical Co.)	Colonoscopy	Sensitivity, specificity, positive and negative predictive values
Ng 2013 (Hong Kong)	Consecutive asymptomatic subjects aged 50–70 years who had both FIT and colonoscopy were recruited between May 2008 and October 2012 from our bowel cancer screening community centre. Individuals were included if they had no symptoms in the past 6 months suggestive of CRC (i.e. haematochezia, melena, anorexia, change in bowel habit or weight loss greater than 5 kg) and no screening test for CRC performed in the past 5 years. **Age mean(SD):** 57.68 (4.86) years **Men/Women:** 45.3%/54.7% **N = 3967 (average risk)** **N = 572 (FH risk)**	Diagnostic accuracy	iFOBT Hemosure (WHPM, Inc., El Monte, CA, USA)	Colonoscopy	Sensitivity, Specificity, PPV, NPV
Omata 2011 (Japan)	A total of 3194 consecutive asymptomatic Japanese individuals voluntarily underwent a general health checkup between 1 May 2004 and 30 June 2008 at a tertiary referral center in Tokyo, Japan, of whom 2153 underwent colonoscopy. A total of 1068 individuals were excluded from the study: 973 had previous colonoscopy, 11 had incomplete colonoscopy, and QTFIT results were unavailable in 84 patients. We analyzed the remaining 1085 consecutive individuals who completed both full colonoscopy and QTFIT testing. **Age mean(SD):** 64(11) years **Men/Women:** 69.7%/30.3% **N = 1085**	Diagnostic accuracy	QTFIT OCMicro instrument (Eiken Chemical Co., Tokyo, Japan).	Colonoscopy	Sensitivity, Specificity, PPV, NPV, PLR, NLR, AUC

N = number of participants; SD = standard deviation; CRC = colorectal cancer; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; QT = quantitative; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio; AUC = area under the curve

Table 8: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Park 2010 (South Korea)	Asymptomatic, average-risk people between 50 and 75 years of age who underwent screening colonoscopy from four tertiary medical centers (Kangbuk Samsung Hospital, Samsung Medical Center, Hanyang University Guri Hospital, and Soonchunhyang University Hospital) in South Korea were invited to participate in the study. **Age mean(SD):** 59.3(7.5) years **Men/Women:** 51.4%/48.6% **N = 770**	Diagnostic accuracy	iFOBT (OC-SENSA MICRO; Eiken Chemical, Tokyo, Japan) gFOBT (hemoccult II test; Beckman Coulter, Fullerton, California),	Colonoscopy	ROC sensitivity, specificity, PLR, NLR, NNT
Parra-Blanco 2010 (Spain)	From January 2004 to August 2006, 3092 subjects (1062 males, 2030 females) were randomly selected (stratifying by age and sex) from among 71673 inhabitants aged 50-79 years in the north area of Tenerife, Spain. Among them, 804 (25.6%) were excluded for different reasons, therefore, 2288 (74%) subjects were finally included. **Age mean(SD):** 62.7(7.4) years **Men/Women:** 32.8%/67.2% **N = 402**	Diagnostic accuracy	gFOBT (Hemofec, Roche) iFOBT (LA-FOBT, OC-LightTM, Eiken Chemical Co., Ltd., Japan)	Colonoscopy	Sensitivity, Specificity, PPV, NPV
Redwood 2016 (Alaska)	The target population comprised asymptomatic persons with any degree of self-reported Alaskan Native heritage who were 40 through 85 years old, were scheduled for average-risk screening or surveillance colonoscopy at the Alaska Native Medical Center (ANMC) in Anchorage, Alaska, and were able to give informed consent. **Age mean(IQR):** 52 (50-59) years (screening) **Age mean(IQR):** 59 (54-64) years (surveillance) **Men/Women:** 39%/61% **N = 435 (screening)** **N = 226 (surveillance)** **N = 661 (total)**	prospective cross-sectional study	Multitarget stool DNA test (KRAS mutations, 2 methylated genes (NDRG4 and BMP3) and b-actin) (Cologuard, Wisconsin, United States) iFOBT (OCSensor Diana, PolyMedco, Portlandt, New York)	Colonoscopy	Sensitivity, Specificity

N = number of participants; SD = standard deviation; CRC = colorectal cancer; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; gFOBT = guaiac faecal occult blood test; DNA = deoxyribonucleic acid; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver operating characteristic

Table 9: Diagnostic accuracy studies assessing faecal or blood tests for the diagnosis of advanced adenomas or CRC in a screening population.

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Terhaar 2011 (Netherlands)	All ambulatory subjects over the age of 40 years scheduled to undergo elective colonoscopy from June 2006 to January 2009 at 1 of the 5 participating hospitals were invited to participate in this study. **Age mean(range):** 61.8 (40-89) years **Men/Women:** 46.2%/53.8% **N = 2,145**	Diagnostic accuracy	iFOBT OC-sensor test (Eiken Chemical Co.).	Colonoscopy	Sensitivity, Specificity
Viana-Freitas 2013 (Brazil)	All consecutive patients scheduled for elective colonoscopy at our university hospital endoscopy unit from July 2009 to July 2010 were invited to bring a stool sample on the day of the educational session about colonoscopy, which takes place one week before the exam. All patients who underwent colonoscopy and provided the stool sample were initially included in the study. **Age mean(SD):** 56(14) years **Men/Women:** 35.8%/64.2% **N = 302**	Diagnostic accuracy	Feca-Cult One Step iFOBT (Alamar Tecno Cient´ıfica Ltd)	Colonoscopy	Sensitivity, Specificity, PPV, NPV,

N = number of participants; SD = standard deviation; iFOBT = immunochemical faecal occult blood test; PPV = positive predictive value; NPV = negative predictive value

Table 10. Diagnostic accuracy studies reported in the 2009 Ontario HTA and 2016 USPSTF Colorectal Cancer Screening Guideline

Study	Participants	Design	Index test(s)	Reference test	Accuracy measures
Graser 2009 (Germany)	Participants had to be 50 years of age and free of symptoms of colonic diseases such as melaenic stools, haematochezia, diarrhoea, relevant changes in stool frequency or abdominal pain. **Age mean (SD):** 60.5 (7.0) years **Men/Women:** 55%/45% **FIT = 285**	Diagnostic accuracy	iFOBT (FOB Gold – Sentinal Diagnostics, Milan, Italy)	Colonoscopy	Sensitivity, Specificity, PPV, NPV for advanced adenoma
Lee 2015 (Korea)	The study population consisted of 1397 individuals who received annual physical check-up at the Gangnam branch of Korean Association of Health Promotion (KAHP), during the period between July 2012 and March 2013. Age range 50-76 years. **Age median:** 58 years **Men/Women:** 48%/52% **N = 1397**	Diagnostic accuracy	iFOBT (NS-Plus C)	Colonoscopy	Sensitivity, Specificity, AUC of ROC
Morikawa 2005 (Japan)	Retrospective analysis of an existing dataset from patients who participated in a comprehensive health examination program at Kameda General Hospital or Kameda Makuhari Clinic between April 1983 and March 2002. All eligible patients were asymptomatic and participated voluntarily in this program. **Age mean (SD):** 48.2±9.3 years **Men/Women:** 72%/28% **N = 21,805**	Diagnostic accuracy	iFOBT (Fujirebio Inc.) Only collected 1 faecal sample and not 2 samples per participant.	Colonoscopy	Sensitivity, Specificity
Nakazato 2006 (Japan)	Asymptomatic adults who underwent both a colonoscopic examination and an iFOBT, independently performed in a single day in complete medical check-up conducted at our hospital in the period from July 1998 through July 2002. **Age mean(range):** not reported **Men/Women:** not reported **N = 3,090**	Diagnostic accuracy	iFOBT (unspecified)	Colonoscopy	Sensitivity, Specificity, PPV, NPV

N = number of participants; SD = standard deviation; FIT = faecal immunochemical test; iFOBT = immunochemical faecal occult blood test; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; ROC = receiver operating characteristic

2.5 Study risk of bias

Table 11: Methodological risk of bias in included diagnostic studies (n = 29)

Risk of bias categories	N (%)
I. Selection of participants	
Low risk of bias	23 (80%)
High risk of bias	3 (10%)
Unclear risk of bias	3 (10%)
II. Index test 1	
Low risk of bias	17 (59%)
High risk of bias	0 (0%)
Unclear risk of bias	12 (41%)
III. Index test 2	
Low risk of bias	7 (25%)
High risk of bias	0 (0%)
Unclear risk of bias	3 (10%)
Not applicable	19 (65%)
IV. Reference standard	
Low risk of bias	21 (72%)
High risk of bias	0 (0%)
Unclear risk of bias	8 (28%)
Not applicable	0 (0%)
V. Flow and timing	
Low risk of bias	11 (38%)
High risk of bias	10 (34%)
Unclear risk of bias	8 (28%)
Not applicable	0 (0%)

Table 12: Risk of bias summary assessment in individual included diagnostic studies (n = 29)

Study	Patient selection	Index test 1	Index test 2	Reference standard	Flow and timing	Overall risk of bias
Ahlquist 2008	HIGH	LOW	LOW	LOW	HIGH	**AT RISK**
Annahazi 2016	UNCLEAR	UNCLEAR	N/A	UNCLEAR	LOW	**AT RISK**
Brenner 2010	UNCLEAR	LOW	N/A	LOW	HIGH	**AT RISK**
Brenner 2013	LOW	UNCLEAR	LOW	LOW	LOW	**AT RISK**
Castro 2014	LOW	LOW	LOW	LOW	UNCLEAR	**AT RISK**
Chen 2014	LOW	LOW	N/A	LOW	UNCLEAR	**AT RISK**
Chiu 2013	LOW	LOW	N/A	LOW	HIGH	**AT RISK**
Church 2014	LOW	UNCLEAR	N/A	UNCLEAR	LOW	**AT RISK**
De Wijkerslooth 2012	LOW	UNCLEAR	N/A	LOW	LOW	**AT RISK**
Elsafi 2015	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	**AT RISK**
Gimeno-Garcia 2009	LOW	LOW	N/A	LOW	LOW	**LOW RISK**
Graser 2009	LOW	UNCLEAR	N/A	UNCLEAR	HIGH	**AT RISK**
Hernandez 2014	LOW	LOW	N/A	LOW	LOW	**LOW RISK**
Hundt 2009	LOW	LOW	N/A	LOW	LOW	**LOW RISK**
Imperiale 2014	HIGH	LOW	LOW	LOW	HIGH	**AT RISK**
Kato 2009	LOW	UNCLEAR	N/A	LOW	HIGH	**AT RISK**
Lee 2013	LOW	LOW	LOW	UNCLEAR	LOW	**AT RISK**
Lee 2015	UNCLEAR	LOW	N/A	LOW	UNCLEAR	**AT RISK**
Levy 2014	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	**AT RISK**
Khalid-de Bakker 2011	LOW	UNCLEAR	N/A	UNCLEAR	HIGH	**AT RISK**
Morikawa 2005	LOW	UNCLEAR	N/A	LOW	HIGH	**AT RISK**
Nakazako 2006	LOW	UNCLEAR	N/A	UNCLEAR	UNCLEAR	**AT RISK**
Ng 2013	LOW	LOW	N/A	LOW	LOW	**LOW RISK**
Omata 2011	LOW	LOW	N/A	LOW	UNCLEAR	**AT RISK**
Park 2010	LOW	LOW	LOW	LOW	HIGH	**AT RISK**
Parra-Blanco 2010	LOW	LOW	UNCLEAR	LOW	UNCLEAR	**AT RISK**
Redwood 2016	LOW	LOW	LOW	LOW	HIGH	**AT RISK**
Terhaar 2011	LOW	LOW	N/A	LOW	LOW	**LOW RISK**
Viana-Freitas 2013	LOW	UNCLEAR	N/A	LOW	LOW	**AT RISK**

Key to overall risk of bias rating

Low risk of bias: A study rated at low risk of bias for all domains
At risk of bias: A study rated at high or unclear risk of bias for one or more domains

2.6 OUTCOMES

Table 13: Results of studies examining diagnostic accuracy of detecting colorectal neoplasms by screening tests

Study	Study characteristics			Index test		Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC of ROC	AUC 95% CI	p value (AUC)
	Total (n)	Neoplasm	DR (%)	(brand)		%	%	(%)	(%)					
Ahlquist 2008	2497	Colorectal cancer	0.5	Stool DNA test 1		25	96	6	99	6.25	0.78	NR	NR	NR
	217		8.8	Stool DNA test 2		58	84	48	89	3.63	0.50	NR	NR	NR
	2497	Adenoma (≥ 1cm)	5.4	Stool DNA test 1		17	96	28	93	4.25	0.86	NR	NR	NR
	217		47.5	Stool DNA test 2		46	84	80	53	2.88	0.64	NR	NR	NR
Annahazi 2016	109	Colorectal cancer	25.7	Faecal MMP-9 protein level		89.3	91.2	71.4	97.1	10.1	0.12	0.913	0.83-0.99	<0.001
		High-risk adenomas	NR			NR	NR	-	-	-	-	0.670	0.51-0.83	0.033
		High-risk adenomas and Colorectal cancer	NR			76	85.3	NR	NR	5.17	0.28	0.806	0.71-0.90	<0.001
Brenner 2010	**Total** 2324 **Men** 1157 **Women** 1167	Advanced Colorectal neoplasms	**Total** 10.5% **Men** 13.5% **Women** 7.5%	immoCARE-C	All	28.4	95.2	38.3	92.7	5.93	0.75	NR	NR	NR
					Men	32.9	93.9	45.5	90.0	5.39	0.71	NR	NR	NR
					Women	20.5	96.5	32.1	93.7	5.86	0.82	NR	NR	NR
				FOB advanced	All	33.7	87.9	22.5	92.7	2.78	0.75	NR	NR	NR
					Men	37.0	85.3	28.0	89.8	2.52	0.74	NR	NR	NR
					Women	28.1	90.4	18.7	94.1	2.93	0.80	NR	NR	NR
				PreventID CC	All	49.0	84.3	24.6	94.0	3.11	0.61	NR	NR	NR
					Men	51.0	81.1	29.5	91.4	2.70	0.60	NR	NR	NR
					Women	45.5	87.4	22.7	95.2	3.61	0.62	NR	NR	NR
				Bionexia FOBplus	All	48.2	83.0	22.8	93.9	2.83	0.63	NR	NR	NR
					Men	49.7	79.2	27.0	91.0	2.39	0.64	NR	NR	NR
					Women	45.5	86.7	21.9	95.1	3.42	0.63	NR	NR	NR
				QuickVue iFOB	All	53.6	73.0	17.2	93.8	1.98	0.64	NR	NR	NR
					Men	59.6	68.4	22.7	96.1	1.89	0.59	NR	NR	NR
					Women	43.0	77.5	13.6	94.3	1.91	0.74	NR	NR	NR
				Bionexia Hb/Hp Complex	All	68.9	58.4	14.8	94.7	1.66	0.53	NR	NR	NR
					Men	72.1	53.0	19.1	92.5	1.53	0.53	NR	NR	NR
					Women	63.4	63.8	12.6	95.5	1.75	0.57	NR	NR	NR

*N -number of participants; DR – detection rate; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; ROC - receiver operating characteristic; CRC – colorectal cancer; CI – confidence interval; NR – not reported; FIT - faecal immunochemical test; MMP-9 - Matrix Metallopeptidase-9 ; DNA Deoxyribonucleic acid; Hb-Hp – haemoglobin-haptoglobin; Hb - haemoglobin**;** Annahazi 2016 – definition for high-risk adenoma was polyp size >10 mm; villous adenoma or tubulovillous adenoma with at least 20% villous component; high-grade dysplasia; or multiple adenoma.*

Table 14: Results of studies examining diagnostic accuracy of detecting colorectal neoplasms by screening tests

Study	Study characteristics			Index test		Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC of ROC	AUC 95% CI	p value (AUC)
	Total (n)	Neoplasm	DR (%)	(brand)		(%)	(%)	(%)	(%)					
Brenner 2013	2235	Colorectal cancer	0.7	RIDASCREEN Hb		60.0	95.4	8.1	99.7	13.06	0.42	NR	NR	NR
				RIDASCREEN Hb-Hp		53.3	95.4	7.3	99.7	11.61	0.49	NR	NR	NR
				OC SENSOR		73.3	95.5	10.0	99.8	16.44	0.28	NR	NR	NR
		Advanced neoplasia	9.3	RIDASCREEN Hb		23.4	97.1	46.9	92.8	7.99	0.79	NR	NR	NR
				RIDASCREEN Hb-Hp		20.3	96.8	40.9	91.7	6.28	0.82	NR	NR	NR
				OC SENSOR		25.7	97.4	51.8	92.2	9.75	0.76	NR	NR	NR
Castro 2014	595	Colorectal cancer	1.0	FIT1		100	95.25	17.65	100	13.09	-	0.96	0.95-0.98	NR
				FIT_{max}		100	93.21	13.04	100	21.04	-	0.95	0.93-0.97	NR
		Advanced neoplasia	9.7	FIT1		39.06	98.31	73.53	93.05	23.05	0.62	0.74	0.66-0.82	NR
				FIT_{max}		43.75	96.61	60.87	93.44	12.91	0.58	0.74	0.66-0.82	NR
Chen 2014	6096	Invasive cancer	0.2	iFOBT	≥40 years	69.2	97.3	6.7	99.9	25.39	0.32	NR	NR	NR
Accuracy					40-49 years	60.0	97.9	7.1	99.9	28.12	0.41	NR	NR	NR
					≥50 years	75.0	96.9	6.5	99.9	24.02	0.26	NR	NR	NR
					50-75 years	75.0	96.9	6.6	99.9	24.04	0.26	NR	NR	NR
					>75 years	NA	96.7	NA	NA	NA	NA	NR	NR	NR
		Advanced neoplasia	4.2		≥40 years	22.0	97.3	30.8	95.8	8.08	0.80	NR	NR	NR
					40-49 years	32.1	97.9	31.6	97.9	15.12	0.69	NR	NR	NR
					≥50 years	19.2	96.9	30.4	94.4	6.15	0.83	NR	NR	NR
					50-75 years	18.8	96.9	29.8	94.4	6.01	0.84	NR	NR	NR
					>75 years	33.3	96.7	50.0	93.7	10.17	0.89	NR	NR	NR

N - number of participants; DR – detection rate; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; ROC - receiver operating characteristic; CRC – colorectal cancer; CI – confidence interval; NR – not reported; FIT - faecal immunochemical test; Hb-Hp – haemoglobin-haptoglobin; iFOBT - immunochemical faecal occult blood test.

Table 15: Results of studies examining diagnostic accuracy of detecting colorectal neoplasms by screening tests

Study	Study characteristics			Index test		Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC of ROC	AUC 95% CI	p value (AUC)
	Total (n)	Neoplasm	DR (%)	(brand)		(%)	(%)	(%)	(%)					
Chiu 2013	18296	Cancer	0.15	iFOBT		78.6	92.8	1.65	99.9	10.9	0.23	NR	NR	NR
		Advanced adenoma	3.5			28.0	93.5	13.3	97.3	4.3	0.77	NR	NR	NR
Church 2014	1510	Colorectal cancer	3.5	Plasma methylated SEPT9 DNA	All	50.9	91.4	17.6	98.1	5.89	0.54	NR	NR	NR
	1006		1.8		<65 years	55.6	92.3	11.6	99.1	7.22	0.48	NR	NR	NR
	504		6.9		≥65 years	48.6	89.3	25.4	95.9	4.56	0.58	NR	NR	NR
	689		5.1		Men	48.6	90.8	22.1	97.1	5.30	0.57	NR	NR	NR
	821		2.2		Women	55.6	91.8	13.2	98.9	6.76	0.48	NR	NR	NR
	1510	Advanced adenoma	20.8		All	9.6	91.4	27.3	75.0	1.12	0.99	NR	NR	NR
	1006		18.8		<65 years	7.9	92.6	23.4	77.9	1.07	0.99	NR	NR	NR
	504		24.8		≥65 years	12.0	88.6	32.6	68.6	1.05	0.99	NR	NR	NR
	689		26.7		Men	13.0	92.3	46.2	67.7	1.69	0.94	NR	NR	NR
	821		15.8		Women	4.6	90.9	10.3	80.7	0.51	1.05	NR	NR	NR
De Wijkerslooth 2012	1256	Colorectal cancer	0.6	iFOBT	≥50 ng/mL	88	91	6	100	9.6	0.14	NR	NR	NR
					≥75 ng/mL	75	93	7	100	11.4	0.27	NR	NR	NR
					≥100 ng/mL	75	95	8	100	14.4	0.26	NR	NR	NR
		Advanced adenoma	9		≥50 ng/mL	35	93	33	94	5.0	0.70	NR	NR	NR
					≥75 ng/mL	31	95	40	93	6.7	0.72	NR	NR	NR
					≥100 ng/mL	29	97	46	93	8.8	0.73	NR	NR	NR
Elsafi 2015	257	Colorectal cancer	1.6	iFOBT (RAPEPKT313)		75	90.12	10.71	99.56	7.59	0.28	NR	NR	NR
Gimeno-Garcia 2009	116	Advanced adenoma	10.3	LA-FOBT		83.3	91.3	52.6	97.9	9.57	0.18	NR	NR	NR
Hernandez 2014	779	Invasive cancer	0.6	FIT1		100	94	10	100	16.86	-	0.97	NR	NR
				FIT_{max}		100	90	6	10	10.46	-	0.95	NR	NR
		Advanced neoplasia	11.2	FIT1		30	97	57	99	9.27	0.72	0.72	NR	NR
				FIT_{max}		36	94	44	99	5.59	0.68	0.73	NR	NR

N - number of participants; DR – detection rate; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; ROC - receiver operating characteristic; CRC – colorectal cancer; CI – confidence interval; NR – not reported; FIT - faecal immunochemical test; SEPT9 – Septin 9; DNA Deoxyribonucleic acid; Hb-Hp – haemoglobin-haptoglobin; Hb - haemoglobin.

Table 16: Results of studies examining diagnostic accuracy of detecting colorectal neoplasms by screening tests

Study	Study characteristics			Index test	Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC of ROC	AUC 95% CI	p value (AUC)
	Total (n)	Neoplasm	DR (%)	(brand)	(%)	(%)	(%)	(%)					
Hundt 2009	1319	Advanced adenoma	9.9	Bionexia FOB+	52.3	81.9	29.2	92.4	2.90	0.58	NR	NR	NR
				Bionexia Hb/Hp	71.5	58.8	19.8	93.6	1.73	0.48	NR	NR	NR
				PreventID CC	49.2	81.8	27.8	91.9	2.71	0.62	NR	NR	NR
				immoCARE-C	25.4	96.7	52.4	90.1	7.73	0.77	NR	NR	NR
				FOB advanced	26.9	92.9	35.0	89.9	3.79	0.79	NR	NR	NR
				QuickVue iFOB	56.2	70.2	21.2	91.8	1.89	0.63	NR	NR	NR
Imperiale 2014	9989	Colorectal cancer	0.65	Multitarget DNA	92.3	86.6	4.6	99.9	6.87	0.09	0.94	NR	NR
				iFOBT	73.8	94.9	9.2	99.8	14.34	0.28	0.89	NR	NR
		Advanced precancerous lesions[a]	7.6	Multitarget DNA	42.4	86.6	20.7	94.8	3.16	0.66	0.73	NR	NR
				iFOBT	23.8	94.9	27.6	93.8	4.62	0.80	0.67	NR	NR
Kato 2009	21794	Advanced neoplasia	1.5	iFOBT	22.3	94.6	5.8	98.8	4.13	0.82	NR	NR	NR
		Colorectal cancer	0.11		58.3	94.5	1.1	100	10.6	0.44	NR	NR	NR
Lee 2013	3172	Colorectal cancer	1.2	iFOBT	82.1	96.8	25.45	0.19	25.7	0.19	NR	NR	NR

N -number of participants; [a]Advanced precancerous lesions include advanced adenomas and sessile serrated polyps measuring ≥1 cm; DR – detection rate; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; ROC - receiver operating characteristic; CRC – colorectal cancer; CI – confidence interval; NR – not reported; FIT - faecal immunochemical test; iFOBT – immunochemical faecal occult blood test; SEPT9 – Septin 9; DNA Deoxyribonucleic acid.

Table 17: Results of studies examining diagnostic accuracy of detecting colorectal neoplasms by screening tests

Study	Study characteristics			Index test		Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC of ROC	AUC 95% CI	p value (AUC)
	Total (n)	Neoplasm	DR (%)	(brand)		(%)	(%)	(%)	(%)					
Levy 2014	44	Advanced adenomas or cancer	NR	Inverness Clearview		20	92	25	90	2.60	0.87	NR	NR	NR
	308		NR	Alere Clearview		13	86	5	95	0.98	1.00	NR	NR	NR
	217		NR	Polymedco OC-Light		5	99	33	92	5.21	0.96	NR	NR	NR
	52		NR	Quidel QuickVue		50	88	14	98	4.16	0.57	NR	NR	NR
Khalid-de Bakker 2011	329	Advanced adenomas	11.6	iFOBT	All	15.8	96.9	40	89.8	5.097	0.869	NR	NR	NR
	192		9.9		Women	5.3	97.7	20.0	90.4	2.304	0.969	NR	NR	NR
	137		13.9		Men	26.3	95.8	50.0	89.0	6.262	0.769	NR	NR	NR
	NR		NR		<55y	9.5	96.7	28.6	88.6	2.879	0.936	NR	NR	NR
	NR		NR		≥55y	23.5	97.1	50.0	91.2	8.103	0.788	NR	NR	NR
Ng 2013 (Av risk)	3967	Advanced neoplasm	4.6	iFOBT		39.6	90.5	16.6	96.9	4.168	0.667	NR	NR	NR
		Colorectal cancer	0.5			61.1	89.3	2.5	99.8	5.710	0.436	NR	NR	NR
Ng 2013 (FH of CRC)	572	Advanced neoplasm	6.5			35.1	91.4	22.0	95.3	4.081	0.710	NR	NR	NR
		Colorectal cancer	0.7			25.0	89.8	1.7	99.4	2.451	0.835	NR	NR	NR
Omata 2011	1085	Significant neoplasia	6.5	iFOBT 25ng/mL c-off		51	77	13	96	2.21	0.64	0.68	0.61-0.75	NR
		Colorectal cancer	0.7	iFOBT 50ng/mL c-off		75	86	4	99.8	5.39	0.29	0.81	0.64-0.98	NR
Park 2010	770	Advanced adenoma	7.7	qFIT (100 ng/mL cut off)		33.9	90.6	23.0	94.3	3.6	0.7	0.723	NR	NR
		Cancer	1.7			92.3	90.1	13.8	99.9	9.3	0.1	0.887	NR	NR
Parra-Blanco 2010	402	Advanced adenoma	12.2	LA-FOBT		56.8	94.5	3.65	97.5	10.3	0.46	NR	NR	NR
		Invasive cancer	3.5			100	92.7	10.8	100	13.7	-	NR	NR	NR
Redwood 2016	661	Colorectal cancer	1.5	MT-sDNA		100	91	NR	NR	NR	NR	NR	NR	NR
				iFOBT		80	94	NR	NR	NR	NR	NR	NR	NR
		Advanced adenoma	11.5	MT-sDNA		41	91	NR	NR	NR	NR	NR	NR	NR
				iFOBT		22	94	NR	NR	NR	NR	NR	NR	NR
Terhaar 2011	2145	Colorectal cancer	3.7	iFOBT (50 ng/mL cut-off)		92.4	86.4	20.6	99.7	6.79	0.09	0.93	0.89-0.96	NR
		Advanced adenoma	11.0			41.1	89.9	34.5	92.2	4.09	0.66	0.69	0.65-0.73	NR
Viana 2013	302	Colorectal cancer	2.9	iFOBT		88.9	87.6	18.6	99.6	7.17	0.13	NR	NR	NR
		Advanced adenoma	3.6			63.6	87.6	16.7	98.4	5.13	0.42	NR	NR	NR

N- number of participants; DR – detection rate; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; ROC - receiver operating characteristic; CRC – colorectal cancer; CI – confidence interval; NR – not reported; FIT - faecal immunochemical test; DNA Deoxyribonucleic acid; FH – family history; Ng 2013 definition for advanced neoplasm: ≥10 mm in diameter, having a villous or tubulovillous component, or high grade dysplastic lesions or carcinoma in situ.

Table 18: Results of studies examining diagnostic accuracy of detecting colorectal neoplasms by screening tests

Study	Study characteristics			Index test	Sensitivity	Specificity	PPV	NPV	PLR	NLR	AUC of ROC	AUC 95% CI	p value (AUC)
	Total (n)	Neoplasm	DR (%)	(brand)	(%)	(%)	(%)	(%)					
Graser 2009	307	Advanced adenoma	9.8	iFOBT (FOB Gold)	32.0	85.8	17.8	92.9	NR	NR	NR	NR	NR
Lee 2015	1397	Colorectal cancer and/or advanced adenoma	1.5	iFOBT (NS-Plus C)	76.2	94.3	NR	NR	NR	NR	0.854	0.83-0.87	<0.0001
		Colorectal cancer	1.0		85.7	94.0	NR	NR	NR	NR	0.907	0.89-0.92	<0.0001
Morikawa[a] 2005	21,805	Colorectal cancer	0.4	iFOBT (Fujirebio)	65.8	94.6	NR	NR	NR	NR	NR	NR	NR
		Advanced adenoma	2.4		20.0	NR	NR	NR	NR	NR	NR	NR	NR
Nakazako 2006	3090	Colorectal cancer	0.6	iFOBT	52.6	87.2	2.5	99.7	NR	NR	NR	NR	NR
		Advanced adenoma	1.7		24.5	87.1	3.2	98.5	NR	NR	NR	NR	NR

N -number of participants; DR – detection rate; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; ROC - receiver operating characteristic; CI – confidence interval; NR – not reported; iFOBT - immunochemical faecal occult blood test [a]The investigators did not follow manufacturer's recommendation and collected only one faecal sample, not two. The reported sensitivity figures are therefore likely to be under-estimates of the true sensitivity for this test.

Body of Evidence

Table 19: Results of studies examining diagnostic accuracy at detecting colorectal cancer using screening tests in an average risk population

Name of study	Study type	Level of evidence	Risk of bias	N	Test (brand)		Diagnostic Accuracy results						
							Sen	Spec	PPV	NPV	PLR	NLR	AUC
Detection of colorectal cancer by immunochemical FOBT (iFOBT)													
Chiu 2013	DA	II	At Risk	18296	iFOBT (OC-Light)		78.6	92.8	1.65	99.9	10.9	0.23	NR
Parra-Blanco 2010	DA	III-1	At Risk	402	iFOBT (OC-Light)		100	92.7	10.8	100	13.7	-	NR
Chen 2014	DA	II	At Risk	6096	iFOBT (OC-Light)	≥40 years	69.2	97.3	6.7	99.9	25.39	0.32	NR
				2214		40-49 years	60.0	97.9	7.1	99.9	28.12	0.41	NR
				3882		≥50 years	75.0	96.9	6.5	99.9	24.02	0.26	NR
				3794		50-75 years	75.0	96.9	6.6	99.9	24.04	0.26	NR
				88		>75 years	NA	96.7	NA	NA	NA	NA	NR
Castro 2014	DA	II	At Risk	595	FIT (OCsensor)		100	95.25	17.65	100	13.09	-	0.96
					FIT_{max} (OCsensor)		100	93.21	13.04	100	21.04	-	0.95
De Wijkerslooth 2012	DA	II	At Risk	1256	iFOBT (OCSensor)	≥50 ng/mL	88	91	6	100	9.6	0.14	NR
						≥75 ng/mL	75	93	7	100	11.4	0.27	NR
						≥100 ng/mL	75	95	8	100	14.4	0.26	NR
Lee 2013	DA	II	At Risk	3172	iFOBT (OCSensor)		82.1	96.8	25.45	0.19	25.7	0.19	NR
Redwood 2016	DA	II	At Risk	661	iFOBT (OCSensor)		80	94	NR	NR	NR	NR	NR
Terhaar 2011	DA	II	Low Risk	2145	iFOBT (OCSensor test)		92.4	86.4	20.6	99.7	6.79	0.09	0.93
Hernandez 2014	DA	II	Low Risk	779	iFOBT (OCSensor)		100	94	10	100	16.86	-	0.97
					FIT_{max} (OCSensor)		100	90	6	10	10.46	-	0.95
Omata 2011	DA	II	At Risk	1085	iFOBT (OCMicro). (50ng/mL c-off)		75	86	4	99.8	5.39	0.29	0.81
Park 2010	DA	II	At Risk	770	iFOBT (OC-MICRO) (100 ng/mL c-off)		92.3	90.1	13.8	99.9	9.3	0.1	0.887
Brenner 2013	DA	II	At Risk	2235	iFOBT (RIDASCREEN Hb)		60.0	95.4	8.1	99.7	13.06	0.42	NR
					iFOBT (RIDASCREEN Hb-Hp)		53.3	95.4	7.3	99.7	11.61	0.49	NR
					iFOBT (OCsensor)		73.3	95.5	10.0	99.8	16.44	0.28	NR
Elsafi 2015	DA	II	At Risk	257	iFOBT (RAPEPKT313)		75	90.12	10.71	99.56	7.59	0.28	NR
Ng 2013	DA	II	Low Risk	3967	iFOBT (Hemosure)		61.1	89.3	2.5	99.8	5.710	0.436	NR
Viana-Freitas 2013	DA	II	At Risk	302	iFOBT (Feca-Cult One Step)		88.9	87.6	18.6	99.6	7.17	0.13	NR
Imperiale 2014	DA	III-1	At Risk	9989	iFOBT (OC FIT-CHEK)		73.8	94.9	9.2	99.8	14.34	0.28	0.89
Kato 2009	DA	II	At Risk	21794	iFOBT (Fujirebio Inc)		58.3	94.5	1.1	100	10.6	0.44	NR
Morikawa 2005	DA	II	At Risk	21805	iFOBT (Fujirebio)		65.8	94.6	NR	NR	NR	NR	NR
Lee 2015	DA	II	At Risk	1397	iFOBT (NS-Plus C)		85.7	94.0	NR	NR	NR	NR	0.907

Nakazako 2006	DA	II	At Risk	3090	iFOBT (unspecified)	52.6	87.2	2.5	99.7	NR	NR	NR

N - number of participants; DA - diagnostic accuracy; DR – detection rate; sen – sensitivity; spec – specisivity; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; NR – not reported; NA - not applicable; iFOBT - immunochemical faecal occult blood test

Table 20: Results of studies examining diagnostic accuracy at detecting colorectal cancer using screening tests in an average risk population

Name of study	Study type	Level of evidence	Risk of bias	N	Test (brand)		Diagnostic Accuracy results						
							Sen	Spec	PPV	NPV	PLR	NLR	AUC
Detection of colorectal cancer by Stool DNA test 1 or Stool DNA test 2													
Ahlquist 2008	DA	III-1	At Risk	2497	Stool DNA test 1		25	96	6	99	6.25	0.78	NR
				217	Stool DNA test 2		58	84	48	89	3.63	0.50	NR
Detection of colorectal cancer by MMP-9 protein													
Annahazi 2016	DA	III-1	At Risk	109	Faecal MMP-9 Protein (ELISA)		89.3	91.2	71.4	97.1	10.1	0.12	0.913
Detection of colorectal cancer by plasma mSEPT-9													
Church 2014	DA	II	At risk	1510	Plasma methylated SEPT9 DNA	All	50.9	91.4	17.6	98.1	5.89	0.54	NR
				1006		<65 years	55.6	92.3	11.6	99.1	7.22	0.48	NR
				504		≥65 years	48.6	89.3	25.4	95.9	4.56	0.58	NR
				689		Men	48.6	90.8	22.1	97.1	5.30	0.57	NR
				821		Women	55.6	91.8	13.2	98.9	6.76	0.48	NR
Detection of colorectal cancer by Multi-target stool DNA test													
Imperiale 2014	DA	III-1	At Risk	9989	Multitarget stool DNA		92.3	86.6	4.6	99.9	6.87	0.09	0.94
Redwood 2016	DA	II	At Risk	661	MT stool-DNA (Cologuard)		100	91	NR	NR	NR	NR	NR

N - number of participants; DA - diagnostic accuracy; DR – detection rate; sen – sensitivity; spec – specisivity; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; NR – not reported; iFOBT - immunochemical faecal occult blood test; DNA = deoxyribonucleic acid

Table 21: Results of studies examining diagnostic accuracy at detecting colorectal cancer and advanced adenomas/neoplasms using screening tests in an average risk population

Name of study	Study type	Level of evidence	Risk of bias	N	Test (brand)		Diagnostic Accuracy results						
							Sen	Spec	PPV	NPV	PLR	NLR	AUC
Detection of colorectal cancer and/or advanced adenomas/neoplasms by immunochemical FOBT (iFOBT)													
Brenner 2010	DA	III-1	At Risk	Total 2324 Men 1157 Women 1167	iFOBT (immoCARE-C)	All	28.4	95.2	38.3	92.7	5.93	0.75	NR
						Men	32.9	93.9	45.5	90.0	5.39	0.71	NR
						Women	20.5	96.5	32.1	93.7	5.86	0.82	NR
					iFOBT (FOB advanced)	All	33.7	87.9	22.5	92.7	2.78	0.75	NR
						Men	37.0	85.3	28.0	89.8	2.52	0.74	NR
						Women	28.1	90.4	18.7	94.1	2.93	0.80	NR
					iFOBT (PreventID CC)	All	49.0	84.3	24.6	94.0	3.11	0.61	NR
						Men	51.0	81.1	29.5	91.4	2.70	0.60	NR
						Women	45.5	87.4	22.7	95.2	3.61	0.62	NR
					iFOBT (Bionexia FOBplus)	All	48.2	83.0	22.8	93.9	2.83	0.63	NR
						Men	49.7	79.2	27.0	91.0	2.39	0.64	NR
						Women	45.5	86.7	21.9	95.1	3.42	0.63	NR
					iFOBT (QuickVue iFOB)	All	53.6	73.0	17.2	93.8	1.98	0.64	NR
						Men	59.6	68.4	22.7	96.1	1.89	0.59	NR
						Women	43.0	77.5	13.6	94.3	1.91	0.74	NR
					iFOBT (Bionexia Hb/Hp)	All	68.9	58.4	14.8	94.7	1.66	0.53	NR
						Men	72.1	53.0	19.1	92.5	1.53	0.53	NR
						Women	63.4	63.8	12.6	95.5	1.75	0.57	NR
Chen 2014	DA	II	At Risk	6096	iFOBT (OC-LIGHT)	≥40 years	22.0	97.3	30.8	95.8	8.08	0.80	NR
				2214		40-49 years	32.1	97.9	31.6	97.9	15.12	0.69	NR
				3882		≥50 years	19.2	96.9	30.4	94.4	6.15	0.83	NR
				3794		50-75 years	18.8	96.9	29.8	94.4	6.01	0.84	NR
				88		>75 years	33.3	96.7	50.0	93.7	10.17	0.89	NR
Ng 2013	DA	II	Low Risk	3967	iFOBT (Hemosure)		39.6	90.5	16.6	96.9	4.168	0.667	NR
Levy 2014	DA	III-1	At Risk	44	iFOBT (Inverness Clearview)		20	92	25	90	2.6	0.87	NR
				308	iFOBT (Alere Clearview)		13	86	5	95	0.98	1.00	NR
				217	iFOBT (Polymedco OC-Light)		5	99	33	92	5.21	0.96	NR
				52	iFOBT (Quidel QuickVue)		50	88	14	98	4.16	0.57	NR
Omata 2011	DA	II	At Risk	1085	iFOBT (QTFIT, OCMicro)		51	77	13	96	2.21	0.64	0.68
Brenner 2013	DA	II	At Risk	2235	iFOBT (RIDASCREEN Hb)		23.4	97.1	46.9	92.8	7.99	0.79	NR
					iFOBT (RIDASCREEN Hb-Hp)		20.3	96.8	40.9	91.7	6.28	0.82	NR
					iFOBT (OCsensor)		25.7	97.4	51.8	92.2	9.75	0.76	NR
Castro 2014	DA	II	At Risk	595	FIT1 (OCsensor)		39.06	98.31	73.53	93.05	23.05	0.62	0.74

					FIT_{max} (OCsensor)	43.75	96.61	60.87	93.44	12.91	0.58	0.74
Hernandez 2014	DA	II	Low Risk	779	FIT1 (OC-sensor)	30	97	57	99	9.27	0.72	0.72
					FIT_{max} (OCsensor)	36	94	44	99	5.59	0.68	0.73
Kato 2009	DA	II	At Risk	21794	iFOBT (Fujirebio Inc)	22.3	94.6	5.8	98.8	4.13	0.82	NR
Lee 2015	DA	II	At Risk	1397	iFOBT (NS-Plus C)	76.2	94.3	NR	NR	NR	NR	0.854
Detection of colorectal cancer and/or advanced adenomas/neoplasms by MMP-9 Protein assay												
Annahazi 2016	DA	III-1	At Risk	109	Faecal MMP-9 protein (Abington)	76	85.3	NR	NR	5.17	0.28	0.806

N - number of participants; DA - diagnostic accuracy; DR – detection rate; sen – sensitivity; spec – specisivity; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; NR – not reported; iFOBT - immunochemical faecal occult blood test

Table 22: Results of studies examining diagnostic accuracy at detecting advanced adenomas using screening tests in an average risk population

Name of study	Study type	Level of evidence *	Risk of bias	N	Test (brand)		Diagnostic Accuracy results						
							Sen	Spec	PPV	NPV	PLR	NLR	AUC
Detection of advanced adenomas by immunochemical FOBT (iFOBT)													
Chiu 2013	DA	II	At Risk	18296	iFOBT (OC-LIGHT)		28.0	93.5	13.3	97.3	4.3	0.77	NR
Parra-Blanco 2010	DA	III-1	At Risk	402	iFOBT (LA-FOBT, OC-LightTM)		56.8	94.5	3.65	97.5	10.3	0.46	NR
De Wijkerslooth 2012	DA	II	At Risk	1256	iFOBT (OCSensor)	≥50 ng/mL	35	93	33	94	5.0	0.70	NR
						≥75 ng/mL	31	95	40	93	6.7	0.72	NR
						≥100 ng/mL	29	97	46	93	8.8	0.73	NR
Khalid-de Bakker 2011	DA	III-1	At Risk	329	iFOBT (OCSensor)	All	15.8	96.9	40	89.8	5.097	0.869	NR
				192		Women	5.3	97.7	20.0	90.4	2.304	0.969	NR
				137		Men	26.3	95.8	50.0	89.0	6.262	0.769	NR
				NR		<55y	9.5	96.7	28.6	88.6	2.879	0.936	NR
				NR		≥55y	23.5	97.1	50.0	91.2	8.103	0.788	NR
Terhaar 2011	DA	II	Low Risk	2145	iFOBT (OCSensor)		41.1	89.9	34.5	92.2	4.09	0.66	0.69
Redwood 2016	DA	II	At Risk	661	iFOBT (OCSensor)		22	94	NR	NR	NR	NR	NR
Park 2010	DA	II	At Risk	770	iFOBT (OC-SENSA MICRO)		33.9	90.6	23.0	94.3	3.6	0.7	0.723
Viana-Freitas 2013	DA	II	At Risk	302	iFOBT (Feca-Cult One Step)		63.6	87.6	16.7	98.4	5.13	0.42	NR
Imperiale 2014	DA	III-1	At Risk	9989	FIT (OC FIT-CHEK)		23.8	94.9	27.6	93.8	4.62	0.80	0.67
Hundt 2009	DA	III-1	Low Risk	1319	iFOBT (Bionexia FOB+)		52.3	81.9	29.2	92.4	2.90	0.58	NR
					iFOBT (Bionexia Hb/Hp)		71.5	58.8	19.8	93.6	1.73	0.48	NR
					iFOBT (PreventID CC)		49.2	81.8	27.8	91.9	2.71	0.62	NR
					iFOBT (immoCARE-C)		25.4	96.7	52.4	90.1	7.73	0.77	NR
					iFOBT (FOB advanced)		26.9	92.9	35.0	89.9	3.79	0.79	NR
					iFOBT (QuickVue iFOB)		56.2	70.2	21.2	91.8	1.89	0.63	NR
Graser 2009	DA	III-1	At Risk	307	iFOBT (FOB Gold)		32.0	85.8	17.8	92.9	NR	NR	NR
Morikawa 2005	DA	II	At Risk	21805	iFOBT (Fujirebio)		20.0	NR	NR	NR	NR	NR	NR
Nakazako 2006	DA	II	At Risk	3090	iFOBT (unspecified)		24.5	87.1	3.2	98.5	NR	NR	NR
Detection of advanced adenomas by Stool DNA test 1/2													
Ahlquist 2008	DA	III-1	At Risk	2497	Stool DNA test 1		17	96	28	93	4.25	0.86	NR
				217	Stool DNA test 2		46	84	80	53	2.88	0.64	NR
Detection of advanced adenomas by faecal MMP-9													
Annahazi 2016	DA	III-1	At Risk	109	Faecal MMP-9 protein (Abington)		NR	NR	-	-	-	-	0.670
Detection of colorectal cancer and advanced adenomas by plasma methylated SEPT9 DNA assay													
Church 2014	DA	II	At Risk	1510	Plasma methylated SEPT9 DNA (Epi proColon)	All	9.6	91.4	27.3	75.0	1.12	0.99	NR
				1006		<65 years	7.9	92.6	23.4	77.9	1.07	0.99	NR
				504		≥65 years	12.0	88.6	32.6	68.6	1.05	0.99	NR
				689		Men	13.0	92.3	46.2	67.7	1.69	0.94	NR
				821		Women	4.6	90.9	10.3	80.7	0.51	1.05	NR

Detection of colorectal cancer and advanced adenomas/neoplasms by multi-target DNA test												
Redwood 2016	DA	II	At Risk	661	MT stool DNA (Cologuard)	41	91	NR	NR	NR	NR	NR
Imperiale 2014	DA	III-1	At Risk	9989	Multi-Target stool DNA	42.4	86.6	20.7	94.8	3.16	0.66	0.73

N - number of participants; DA - diagnostic accuracy; DR – detection rate; sen – sensitivity; spec – specisivity; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; NR – not reported; iFOBT - immunochemical faecal occult blood test

Table 23: Results of studies examining diagnostic accuracy at detecting colorectal cancer or colorectal cancer and advanced adenomas/neoplasms using screening tests in an above average risk population.

Name of study	Study type	Level of evidence	Risk of bias	N	Test (brand)	Diagnostic Accuracy results						
						Sen	Spec	PPV	NPV	PLR	NLR	AUC
Detection of colorectal cancer in an above average risk population by immunochemical FOBT (FIT)												
Castro 2014	DA	II	At Risk	595	FIT1 (OCsensor)	100	95.25	17.65	100	13.09	-	0.96
					FIT_{max} (OCsensor)	100	93.21	13.04	100	21.04	-	0.95
Ng 2013	DA	II	Low Risk	572	iFOBT (Hemosure)	25.0	89.8	1.7	99.4	2.451	0.835	NR
Detection of colorectal cancer and advanced adenomas/neoplasms in an above average risk population by immunochemical FOBT (FIT)												
Castro 2014	DA	II	At Risk	595	FIT1 (OCsensor)	39.06	98.31	73.53	93.05	23.05	0.62	0.74
					FIT_{max} (OCsensor)	43.75	96.61	60.87	93.44	12.91	0.58	0.74
Ng 2013	DA	II	Low Risk	572	iFOBT (Hemosure)	35.1	91.4	22.0	95.3	4.081	0.710	NR
Detection of advanced adenomas in an above average risk population by immunochemical FOBT (FIT)												
Gimeno-Garcia 2009	DA	III-1	Low Risk	166	iFOBT (OC-Light)	83.3	91.3	52.6	97.9	9.57	0.18	NR

N - number of participants; DA - diagnostic accuracy; DR – detection rate; sen – sensitivity; spec – specisivity; PPV – positive predictive value; NPV – negative predictive value; PLP positive likelihood ratio; NLR negative likelihood ratio; AUC area under the curve; NR – not reported; iFOBT - immunochemical faecal occult blood test

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APPENDICES

Appendix A: Search strategies used

For PubMed database:

#	Searches
1	colorectal neoplasms[MeSH Terms] OR intestinal polyps[MeSH Terms] OR ((colon*[tiab] OR colorectal[tiab] OR rectal[tiab] OR rectum[tiab]) AND (precancer*[tiab] OR pre-cancer*[tiab] OR polyp[tiab] OR polyps[tiab] OR neoplasm*[tiab] OR adenoma*[tiab] OR cancer*[tiab] OR dysplasia*[tiab] OR neoplasia*[tiab] OR tumour*[tiab] OR tumor*[tiab])) OR precancerous conditions[MeSH Terms]
2	occult blood[MeSH Terms] OR (faecal occult blood test*[tiab] OR faecal occult blood test*[tiab] OR fobt*[tiab]) OR ((faecal[tiab] OR faecal[tiab]) OR feces[tiab] OR faeces[tiab]) AND (blood[tiab] OR immunochemical[tiab] OR guaiac[tiab])) OR guaiac[MeSH Terms] OR (hemoccult[tiab] OR seracult[tiab] OR coloscreen[tiab] OR colocare[tiab] OR Guaiac[tiab] OR Ez test[tiab] OR HemeSelect[tiab] OR HemoQuant[tiab] OR insure[tiab] OR flexsure*[tiab])
3	sigmoidoscopy[tiab]
4	Colonoscopy[mh] OR colonoscopy[tiab]
5	2 OR 3 OR 4
6	mass screening[mh] OR screen*[tiab]
7	randomized controlled trial[pt] OR controlled clinical trial[pt] OR placebo[tiab] OR randomi?ed[tiab] OR randomly[tiab] OR trial[tiab] OR group[tiab]
8	English[la] AND 2007:3000[dp]
9	1 AND 5 AND 6 AND 7 AND 8

Used the Cochrane sensitivity maximizing filters for identifying randomized controlled trials (http://handbook.cochrane.org, accessed 20/02/2013/ Centre for Reviews and Dissemination systematic review/ meta-analyses strategy 2.(Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. ***BMC Medical Research Methodology*** *12:51)*

ATSI search terms used

#	Searches
1	australia[mh] OR Australia*[tiab]
2	ancestry group, oceanic[mh] OR ancestry groups, oceanic[mh] OR aborigine, australian[mh] OR aborigines, australian[mh] OR australian aborigine[mh] OR australian aborigines[mh] OR aborigin*[tiab] OR indigenous[tiab]
3	1 AND 2
4	torres strait islander*[tiab]
5	3 OR 4
6	colorect*[tiab] OR colon*[tiab] OR rectal*[tiab] OR rectum*[tiab] OR anus*[tiab] OR bowel*[tiab]
7	(cancer*[tiab] OR neoplas*[tiab] OR oncolog*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR colorectal neoplasms[mh] OR colonic neoplasms[mh] OR rectal neoplasms[mh])
8	6 AND 7
9	5 AND 8
10	english[la] AND 2004:3000[dp]
11	9 AND 10

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Embase database:

#	Searches
1	exp colorectal neoplasms/
2	exp Intestinal Polyps/
3	((colon$ or colorectal or rectal or rectum) adj5 (precancer$ or pre-cancer$ or polyp$ or neoplasm$ or adenoma$ or cancer$ or dysplasia$ or neoplasia$ or tumo?r$)).mp.
4	exp Precancerous Conditions/
5	1 OR 2 OR 3 OR 4
6	exp Occult Blood Test/ or exp Occult Blood/
7	(f?ecal occult blood test$ or fobt$).mp.
8	((f?ecal or f?eces) adj2 (blood or immunochemical or guaiac)).mp.
9	exp GUAIAC/
10	(hemoccult or seracult or coloscreen or Colocare or Guaiac or Ez test or HemeSelect or HemoQuant or insure or flexsure$).mp.
11	6 OR 7 OR 8 OR 9 OR 10
12	sigmoidoscopy.ti,ab.
13	exp colonoscopy/ or colonoscopy.ti,ab.
14	11 OR 12 OR 13
15	exp mass screening/ or screen$.ti,ab.
16	Randomized controlled trial/ or controlled clinical trial/ or placebo.ab. or randomi?ed.ab. or randomly.ab. or trial.ab. or groups.ab.
17	5 AND 14 AND 15 AND 16
18	limit 17 to english language
19	limit 18 to yr="2007-Current"
20	animal/ not human/
21	19 NOT 20
22	(journal conference abstract or journal conference paper or journal letter or journal note or letter or note).pt.
23	21 NOT 22

*Used the SIGN filter for identifying randomized controlled trials (*www.sign.ac.uk/methodology/filters.html#systematic *accessed 20/02/2013)*

ATSI search terms used:

#	Searches
1	australia[mh] OR Australia*[tiab]
2	ancestry group, oceanic[mh] OR ancestry groups, oceanic[mh] OR aborigine, australian[mh] OR aborigines, australian[mh] OR australian aborigine[mh] OR australian aborigines[mh] OR aborigin*[tiab] OR indigenous[tiab]
3	1 AND 2
4	torres strait islander*[tiab]
5	3 OR 4
6	colorect*[tiab] OR colon*[tiab] OR rectal*[tiab] OR rectum*[tiab] OR anus*[tiab] OR bowel*[tiab]
7	(cancer*[tiab] OR neoplas*[tiab] OR oncolog*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR colorectal neoplasms[mh] OR colonic neoplasms[mh] OR rectal neoplasms[mh])
8	6 AND 7
9	5 AND 8
10	english[la] AND 2004:3000[dp]
11	9 AND 10

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment database and PsycINFO

#	Searches
1	(colorect$ or colon$ or rectal$ or rectum$ or anus$ or bowel$).ti,ab.
2	(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adeno).ti,ab.
3	1 AND 2
4	hereditary nonpolyposis colorectal cancer/ or colorectal polyp/ or colorectal tumor/ or colorectal cancer/ or colorectal anastomosis/ or colorectal carcinoma/ or colorectal adenoma/ or colorectal.mp. or hereditary colorectal cancer/
5	colon anastomosis/ or colon carcinoma/ or colon polyposis/ or colon adenocarcinoma/ or colon tumor/ or colon.mp. or colon cancer/ or colon adenoma/ or colon carcinogenesis/ or colon polyp/ or familial colon polyposis/
6	rectum cancer/ or rectum tumor/ or rectum anastomosis/ or rectum carcinoma/ or rectum adenoma/ or rectum/ or rectum polyp/ or rectum.mp.
7	4 OR 5 OR 6
8	3 OR 7
9	limit 8 to english language
10	limit 9 to yr="2004-Current"

CINAHL

#	Searches
1	colorectal cancer screening (TX All Text)
2	colonoscopy screening OR FOBT OR FIT OR biomarker (TX All Text)
3	January 2007 – December 2016 (DT Publication Date)
4	English (LA Language)
5	1 AND 2 AND 3 AND 4

Embase

#	Searches
1	exp colorectal neoplasms/
2	exp Intestinal Polyps/
3	((colon$ or colorectal or rectal or rectum) adj5 (precancer$ or pre-cancer$ or polyp$ or neoplasm$ or adenoma$ or cancer$ or dysplasia$ or neoplasia$ or tumo?r$)).mp.
4	exp Precancerous Conditions/
5	1 OR 2 OR 3 OR 4
6	exp Occult Blood Test/ or exp Occult Blood/
7	(f?ecal occult blood test$ or fobt$).mp.
8	((f?ecal or f?eces) adj2 (blood or immunochemical or guaiac)).mp.
9	exp GUAIAC/
10	(hemoccult or seracult or coloscreen or Colocare or Guaiac or Ez test or HemeSelect or HemoQuant or insure or flexsure$).mp.
11	6 OR 7 OR 8 OR 9 OR 10
12	sigmoidoscopy.ti,ab.
13	exp colonoscopy/ or colonoscopy.ti,ab.
14	11 OR 12 OR 13
15	exp mass screening/ or screen$.ti,ab.
16	Randomized controlled trial/ or controlled clinical trial/ or placebo.ab. or randomi?ed.ab. or randomly.ab. or trial.ab. or groups.ab.
17	(5 AND 14 AND 15) NOT 16
18	limit 17 to english language
19	limit 18 to yr="2007-Current"
20	animal/ not human/
21	19 NOT 20
22	(journal conference abstract or journal conference paper or journal letter or journal note or letter or note).pt.
23	21 NOT 22

Appendix B:

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study type
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Appendix B continued:

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points for considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable.
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels, otherwise they will not be of interest to the patient or their carers.
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated.

Adapted from table 1.10 of: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:
Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason for not adopting
2008	American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology	Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008	Did not meet AGREE II assessment threshold
2016	US Preventive Services Task Force	Lin et al., Screening for Colorectal Cancer Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016;315(23):2576-2594	Studies which met the inclusion criteria of this review were included in this systematic review
2008	American College of Gastroenterology	American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	Did not meet AGREE II assessment threshold
2015	Clinical Practice Guidelines in Oncology (NCCN Guidelines)	Colorectal Cancer Screening (version 1.2015)	Did not meet AGREE II assessment threshold
2014	EMSO	Familial Risk–Colorectal Cancer: ESMO Clinical Practice Guidelines	Did not meet AGREE II assessment threshold
2010	International Agency for Research on Cancer	European guidelines for quality assurance in colorectal cancer screening and diagnosis	Studies which met the inclusion criteria of this review were included in this systematic review
2012	Royal Australian College of General Practitioners	Guidelines for preventive activities in general practice, 8th edition.	Did not meet AGREE II assessment threshold
2009	Ontario Health Technology Assessment Series	Faecal Occult Blood Test for Colorectal Cancer Screening An Evidence-Based Analysis	Studies which met the inclusion criteria of this review were included in this systematic review
2013	Toward Optimized Practice	Colorectal Cancer Screening	Did not meet AGREE II assessment threshold

Excluded studies

Study	Reason for exclusion
Abdullah 2012	Inappropriate participants
Adler 2012	Inappropriate study design
Ahmed 2014	Did not report relevant outcomes
AHTA 2010	Review article
Allameh 2011	Review article (use to snowball)
Allison 2007	Inappropriate study design
Aniwan 2016	Inappropriate study design
Barlev 2016	Inappropriate participants
Brenner 2014 Diagn	Inappropriate intervention
Brenner 2015	Inappropriate study design
Bujanda 2013	Inappropriate study design
Burch 2007	Inappropriate intervention
Cassinotti 2012	Inappropriate study design
Castro 2015	Data reported in individual studies
Caviglia 2016	Inappropriate study design
Chiang 2015	Inappropriate study design
Chalkians 2011	Inappropriate study design
Chang 2010	Inappropriate study design
Chen 2012	Inappropriate participants
Chen 2014	Reported studies with an inappropriate study design
Chen 2015	Inappropriate study design
Chen 2016 Emp	Inappropriate study design
Chen 2016 Prop	Inappropriate study design
Chiang 2014	Inappropriate study design
Creeden 2011	Review article (use to snowball)
Crouse 2015	Inappropriate study design
Cruz-Correa 2005	Inappropriate study design
Davenport 2015	Inappropriate study design
Day 2013	Review article (use to snowball)
Denis 2007	Inappropriate intervention
De Meij 2014	Inappropriate participants
DeVos 2009	Inappropriate study design
Dickinson 2015	Review article
Duffy 2014	Review article
Ewald 2007	Inappropriate study design
Faivre 2012	Inappropriate study design
Fraser 2007	Inappropriate study design
Garcia 2012	Inappropriate intervention
Glockner 2009	Inappropriate study design
Guittet 2009	Inappropriate study design
Hamza 2013	Inappropriate study design
Half 2013	Inappropriate study design
Haug 2007	Inappropriate study design
Haug 2010	Data reported in other studies
Haug 2011 Is FOBT	Review article (use to snowball)
Haug 2011 Sensit	Did not report relevant outcomes
Heigh 2014	Inappropriate study design
Hewett 2010	Inappropriate intervention
Hirai 2016	Inappropriate participants
Hol 2009	Inappropriate study design
Huang 2007 Detect	Inappropriate study design
Huang 2007 Hyper	Inappropriate study design
Huang 2014	Contains studies which do not meet the inclusion criteria for several different reasons
Iannone 2016	Review article (use to snowball)

Itzkowitz 2007	Inappropriate study design
Itzkowitz 2008	Inappropriate study design
Jiang 2014	Contains studies with inappropriate study design
Jin 2015	Inappropriate study design
Kadiyska 2015	Review article
Kahi 2009	Inappropriate intervention
Kanaoka 2004	Inappropriate study design
Karl 2008	Inappropriate study design
Khakimov 2015	Conference abstract
Khoshbaten 2014	Inappropriate study design
Koga 2013	Inappropriate study design
Koga 2014	Review article (use to snowball)
Kovarova 2012	Inappropriate participants
Kraus 2015	Inappropriate study design
Kumar 2007	Outdated study
Launois 2014	Contains studies with inappropriate study design
Lee 2014	Includes outdated study(s)
Leen 2014	Inappropriate study design
Lenhard 2005	Inappropriate study design
Leung 2007	Inappropriate study design
Levi 2007	Inappropriate study design
Levi 2011	Inappropriate study design
Li 2012	Includes outdated study(s)
Li 2014	Review article
Lidgard 2013	Inappropriate study design
Lindholm 2008	Inappropriate study design
Link 2010	Inappropriate study design
Loganayagam 2008	Outdated review article
Lumachi 2012	Inappropriate study design
Luo 2011	Includes outdated study(s)
Luo 2013	Inappropriate study design
Maffei 2014	Inappropriate study design
Malik 2016	Review article
Mead 2011	Inappropriate study design
Meng 2012	Inappropriate study design
Mulder 2007	Inappropriate study design
Mulder 2009	Inappropriate study design
Nagasaka-2009	Inappropriate study design
Nichita 2014	Inappropriate study design
Oberwalder 2008	Did not report relevant outcomes
Oono 2010	Inappropriate participants
Oort 2010	Inappropriate participants
Oort 2011	Inappropriate participants
Orntoft 2015	Inappropriate participants
Otero-Estevez 2014	Inappropriate intervention
Parente 2012	Inappropriate participants
Pedersen 2013-	Inappropriate study design
Pedersen 2015-	Inappropriate study design
Perrone 2015	Inappropriate study design
Pucci 2009	Inappropriate study design
Quintero 2014	Inappropriate study design
Raginel 2013	Inappropriate study design
Ravegnini 2015	Inappropriate study design
Redwood 2014	Inappropriate participants
Ren 2015	Review article
Roperch 2013	Inappropriate study design
Rozen 2009	Inappropriate participants
Rozen 2011	Inappropriate participants

Rozen 2012	Inappropriate participants
Rubeca 2011	Inappropriate participants
Salehi 2015	Inappropriate study design
Sawbridge 2014	Review article
Shah 2014	Review article (use to snowball)
Shastri 2008	Inappropriate participants
Shastri 2006	Outdated study
Sheng 2009	Did not report relevant outcomes
Shin 2013	Inappropriate study design
Sobrino-Cosso 2011	Inappropriate participants
Symonds 2015	Review article (use to snowball)
Symonds 2016	Inappropriate participants
Tagore 2004	Review article
Taguchi 2015	Inappropriate study design
Takai 2009	Inappropriate study design
Tanzer 2010-	Inappropriate study design
Tao 2011	Contains studies with the wrong study design or outdated studies.
Tao 2012	Inappropriate study design
Tao 2013 Compara	Inappropriate study design
Tao 2013 Well adju	Inappropriate study design
Teixeira 2015	Inappropriate participants
Tonus 2006	Inappropriate study design
Toth 2012	Inappropriate study design
Tsang 2014	Review article
Uppara 2015	Review article (use to snowball)
van Rossum 2008	Inappropriate study design
van Turenhout 2012	Inappropriate study design
van Turenhout 2014	Inappropriate participants
Vasilyev 2015	Inappropriate participants
Vatandoorst 2016	Review article
von Roon 2007	Outdated review article
von Roon 2011	Did not report relevant outcomes
Wang 2008	Inappropriate study design
Wang 2014	Inappropriate study design
Wang 2015	Inappropriate study design
Warren 2011	Inappropriate study design
Whitlock 2008	Outdated review article/guideline
Wild 2010	Inappropriate study design
Wilson 2006	Did not report relevant outcomes
Wilson 2012	Inappropriate participants
Wu 2014 Screening	Inappropriate study design
Xue 2014	Inappropriate study design
Yadegarazari 2013	Inappropriate study design
Yip 2010	Inappropriate study design
Zeng 2015	Review of studies with inappropriate study design
Zhai 2016	Inappropriate study design
Zhang 2012	Inappropriate participants
Zhang 2016	Inappropriate study design
Zhou 2013	Review of studies with inappropriate study design
Zhu 2010	Review article (use to snowball)
Zhu 2014	Inappropriate study design

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