Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

Supplemental materials:

Table 1: Search strategies

Search Engine	Terms used
EMBASE	#1 Fecal #2 faecal #3 feces #4 #1 OR #2 OR #3 #5 ‘immunochemistry’/exp #6 immunochem* #7 #5 OR #6 #8 #4 AND #7 #9 fit:ab,ti #10 guaiac:ab,ti #11 ‘occult blood’ #12 fobt* #13 fob* #14 ifobt #15 ifob* #16 #6 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #17 insure #18 inform #19 #17 OR #18 (insure OR inform) #20 #16 AND #19 AND (insure OR inform) #21 ‘instant view’ #22 hemoccult #23 immocare #24 flexsure #25 monohaem

	#26 hemosure #27 occultech #28 quickvue #29 clearview #30 hemoquant #31 ‘hema screen’ #32 innovacon #33 ‘oc micro’ #34 ‘oc sensor’ #35 ‘oc hemodia’ #36 ‘oc light’ #37 aimstep #38 magstream #39 immudia #40 #16 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 #41 ‘predictive value’/de #42 ‘sensitivity and specificity’/de #43 ‘laboratory diagnosis’/exp #44 ‘reproducibility’/de #45 ‘reference value’/de #46 ‘diagnostic error’/exp #47 ‘diagnostic test accuracy study’/de #48 ‘diagnostic accuracy’/de #49 ‘diagnostic value’/de #50 ‘standard’/de #51 ‘gold standard’/de #52 ‘observer variation’/de #53 ‘health care quality’/de #54 ‘biomedical technology assessment’/de #55 ‘clinical effectiveness’/de

	#56 ‘clinical indicator’/de #57 ‘medical error’/exp #58 ‘root cause analysis’/de #59 ‘good laboratory practice’/de #60 ‘validation process’/de #61 sensitiv*:ab,ti #62 specificit*:ab,ti #63 ‘predictive value’:ab,ti #64 accurac*:ab,ti #65 (false NEXT/1 positive*):ab,ti #66 (false NEXT/1 negative*):ab,ti #67 (miss NEXT/1 rate*):ab,ti #68 (error NEXT/1 rate*):ab,ti #69 (detection NEXT/1 rate*):ab,ti #70 (diagnostic NEXT/1 yield*):ab,ti #71 (likelihood NEXT/1 ratio*):ab,ti #72 ‘odds ratio’:ab,ti AND diagnosis:ab,ti #73 risk:ab,ti AND diagnosis:ab,ti #74 ‘diagnostic odds ratio’:ab,ti OR‘diagnostic odds ratios’:ab,ti #75 ‘diagnostic accuracy’ #76 ‘reference standard’:ab,ti OR ‘reference standards’:ab,ti #77 #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 #78 #40 AND #77 #79 ‘colon tumor’/exp #80 ‘rectum tumor’/exp #81 ‘intestine polyp’/exp #82 ‘colon polyp’/exp #83 ‘colon cancer’:ab,ti #84 ‘colonic cancer’:ab,ti

	#85 ‘colorectal cancer’:ab,ti #86 ‘colon neoplasm’:ab,ti #87 ‘colonic neoplasm’:ab,ti #88 ‘colorectal neoplasm’:ab,ti #89 adenoma*:ab,ti #90 ‘colon polyp’:ab,ti #91 ‘colonic polyp’:ab,ti #92 ‘colorectal polyp’:ab,ti #93 #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 #94 #78 AND #93 #95 #78 AND #93 AND [english]/lim #96 #78 AND #93 AND [english]/lim NOT ([animals]/lim NOT ([humans]/lim OR ‘patient’/exp)) #97 #78 AND #93 AND [english]/lim NOT ([animals]/lim NOT ([humans]/lim OR ‘patient’/exp)) NOT ‘conference abstract’/it #98 #78 AND #93 AND [english]/lim NOT ([animals]/lim NOT ([humans]/lim OR ‘patient’/exp)) NOT‘conference abstract’/it AND [2008-2012]/py
Pubmed	(((((immunochemi* OR FIT OR guaiac OR "occult blood" OR FOBT* OR FOB* OR ifobt OR iFOB*) OR ((immunochemi* OR FIT OR guaiac OR "occult blood" OR FOBT* OR FOB* OR ifobt OR iFOB*) AND (insure OR inform)) OR ("Instant-view" OR instant view OR hemoccult OR immocare OR flexure OR monohaem OR hemopure OR occlutech OR quickvue OR clearview OR hemoquant OR "Hema screen" OR hema-screen OR innovation OR oc-micro OR "OC Micro" OR oc-sensor OR "OC Sensor" OR "OC-Hemodia" OR "OC Hemodia OR " oc-light "OR " oc light OR kimstep OR mainstream OR immudia)) AND ("2008/01/01"[PDat] : "2012/12/31"[PDat]))) AND (((((“predictive value of tests”[mh] OR “Sensitivity and specificity”[mh] OR “False Negative Reactions"[mh] OR "False Positive Reactions”[mh] OR “Reproducibility of Results”[mh] OR “Reference Values”[mh] OR “Diagnostic Errors”[mh] OR “Reference Standards”[mh] OR “Observer Variation”[mh] OR “Quality Assurance, Health Care”[mh] OR standards[sh] OR sensitiv*[tiab] OR specificit*[tiab] OR predictive value[tiab] OR accurac*[tiab] OR false positive*[tiab] OR false negative*[tiab] OR miss rate*[tiab] OR error rate*[tiab] OR detection rate*[tiab] OR diagnostic yield*[tiab] OR likelihood ratio*[tiab] OR (“odds ratio” AND diagnosis[sh]) OR “diagnostic odds ratio” [tiab] OR “diagnostic odds ratios” [tiab])) AND (((“Colorectal Neoplasms”[mh] OR “Colonic Neoplasms”[mh] OR “Sigmoid Neoplasms”[mh] OR “Rectal Neoplasms”[mh] OR

	“Intestinal Polyps”[mh] OR “Colonic Polyps”[mh] OR “colon cancer”[all fields] OR “colonic cancer”[all fields] OR “colorectal cancer”[all fields] OR “colon neoplasm”[all fields] OR “colonic neoplasm”[all fields] OR “colorectal neoplasm”[all fields] OR adenoma*[all fields] OR “colon polyp”[all fields] OR “colonic polyp”[all fields] OR “colorectal polyp”[all fields] OR“colon cancers”[all fields] OR “colonic cancers”[all fields] OR “colorectal cancers”[all fields] OR “colon neoplasms”[all fields] OR “colonic neoplasms”[all fields] OR “colorectal neoplasms”[all fields] OR“colon polyps”[all fields] OR “colonic polyps”[all fields] OR “colorectal polyps”[all fields])) Filters: Publication date from 2012/01/01 to 2018/05/30 Sort by: PublicationDate

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Table 2: Studies identified by systematic review as eligible that were subsequently included or excluded for systematic review. Exclusions to avoid overlap of study populations

Author	Year	Journal	Country	Included?
Symonds	2015	Clin Gastro Hep	Australia	No
Symonds	2015	Unit Eur Gastro J	Australia	Yes
Wong	2012	Int J Colo Dis	Canada	Yes
Huang	2016	Eur J Cancer	China	No
Launoy	2005	Int J Cancer	France	Yes
Graser	2008	Gut	Germany	Yes
Brenner	2010	Am J Gastro	Germany	No
Brenner	2013	Eur J Cancer	Germany	Yes
Brenner, H	2013	Eur J Cancer	Germany	No
Tao	2013	Aocologica	Germany	No
Chen, H	2016	Clin Gastro Hep	Germany	Yes
Brenner, H	2017	Int J Can	Germany	No
Brenner	2017	Clin Epid	Germany	No
Brenner	2017	Clin Trans Gastro	Germany	No
Brenner	2017	Int J Cancer	Germany	No
Brenner	2018	Clin Epid	Germany	No
Gies	2018	Gastroenterology	Germany	Yes
Levi	2007	Ann Int Med	Israel	Yes
Levi	2011	Int J Cancer	Israel	Yes
Castiglione	2007	Brit J Cancer	Italy	Yes
Itoh	1996	JMedSc	Japan	Yes
Nakama	2001	Eur J Cancer	Japan	Yes
Morikawa	2005	Gastroenterology	Japan	Yes
Nakazato	2006	Jap Med J	Japan	Yes
Sohn	2005	Can Res Treat	Korea	Yes
Park	2010	Am J Gastro	Korea	Yes
Shin	2013	PLoS One	Korea	Yes
Lee	2015	Clin Chem Lab M	Korea	Yes

Kim, N	2016	Dig Dis Sci	Korea	Yes
Jung	2017	J Gastro Hepat	Korea	No
Kim, N	2017	Dig Liver Dis	Korea	Yes
De Wijkerslooth	2012	Am J Gastro	Netherlands	Yes
Stegeman	2013	Int J Cancer	Netherlands	No
Stegeman	2015	Cancer Epi	Netherlands	Yes
Vleugels	2015	Gastroenterology	Netherlands	No
Ijspeert	2016	Gastroenterology	Netherlands	No
Grobbee	2017	Unit Eur Gastro J	Netherlands	No
Haug	2017	Gut	Netherlands	Yes
VanderVlugt	2017	Gastroenterology	Netherlands	Yes
Hernandez	2012	Gastroenterology	Spain	No
Cubiella	2013	Unit Eur Gastro J	Spain	No
Castro	2014	Dig Dis Sci	Spain	No
Cubiella	2014	Unit Eur Gastro J	Spain	No
Hernandez	2014	World J Gastro	Spain	Yes
Castro	2015	Dig Dis Sci	Spain	No
Liu	2003	Hepato-Gastro	Taiwan	Yes
Chen, L	2011	Lancet Onc	Taiwan	Yes
Chiu	2013	Clin Gastro Hep	Taiwan	No
Chen, Y	2014	Adv Dig Med	Taiwan	No
Chen, C	2016	Medicine	Taiwan	Yes
Chen	2018	C Epi Bio Prev	Taiwan	Yes
Aniwan	2017	Asia Pac J Canc	Thailand	Yes
Imperiale	2014	NEJM	USA	Yes
Johnson	2014	PLoS One	USA	Yes
Mzsliwiec	2014	Gastroenterology	USA	No
Doubeni	2016	JABFM	USA	No
Jensen	2016	Ann Int Med	USA	Yes
Redwood	2016	Mayo Cl Proc	USA	Yes
Shapiro	2017	Am J Gastro	USA	Yes

Liles	2018	BMC Cancer	USA	Yes
Selby	2018	Ann Int Med	USA	Yes

Table 3: Studies used to create pooled estimates of cancer and advanced adenoma prevalence, subsequently utilized to estimate prevalence from a theoretical cohort of 100,000 patients

Author	Year	Total screened	Total screened advanced adenomas	Positive tests	Number of cancers	Number advanced adenomas	Without cancer	Without cancer or advanced adenoma
Itoh	1996	27860		1490	89		27771	
Nakama	2000	2460		175	27		2433	
Liu	2003	1387		31	6		1381	
Morikawa	2005	21805	21805	1231	79	648	21726	21078
Sohn	2005	3794	3794	53	12	67	3782	3715
Nakazato	2006	3090		404	19		3071	
Levi	2007	80	80	15	3	15	77	62
Graser	2009	285	285	45	1	24	284	260
Park	2010	770	770	86	13	59	757	698
Wong	2012	1075	1075	94	2	67	1073	1006
De Wijkerslooth	2012	1256	1256	71	8	113	1248	1135
Brenner	2013	2235	2235	110	15	207	2220	2013
Hernandez	2014	779	779	55	5	92	774	682
Johnson	2014	193	193	6	2	25	191	166
Imperiale	2014	9989	9989	695	65	757	9924	9167
Lee	2015	1397	1397	72	14	7	1383	1376
Chen	2016	3466	3466	370	29	354	3437	3083
Shapiro	2017	947	947	28	2	53	945	892
Aniwan	2017	1479	1479	108	14	123	1465	1342
Kim	2017	26316	26316	805	16	154	26300	26146
Liles	2018	2761	2761	116	2	209	2759	2550
		85564	78627	4570	334	2974	85230	75371
			CRC prev	0.390%				
			AA prev	3.782%				

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Figure 1: PRISMA flow chart detailing study selection

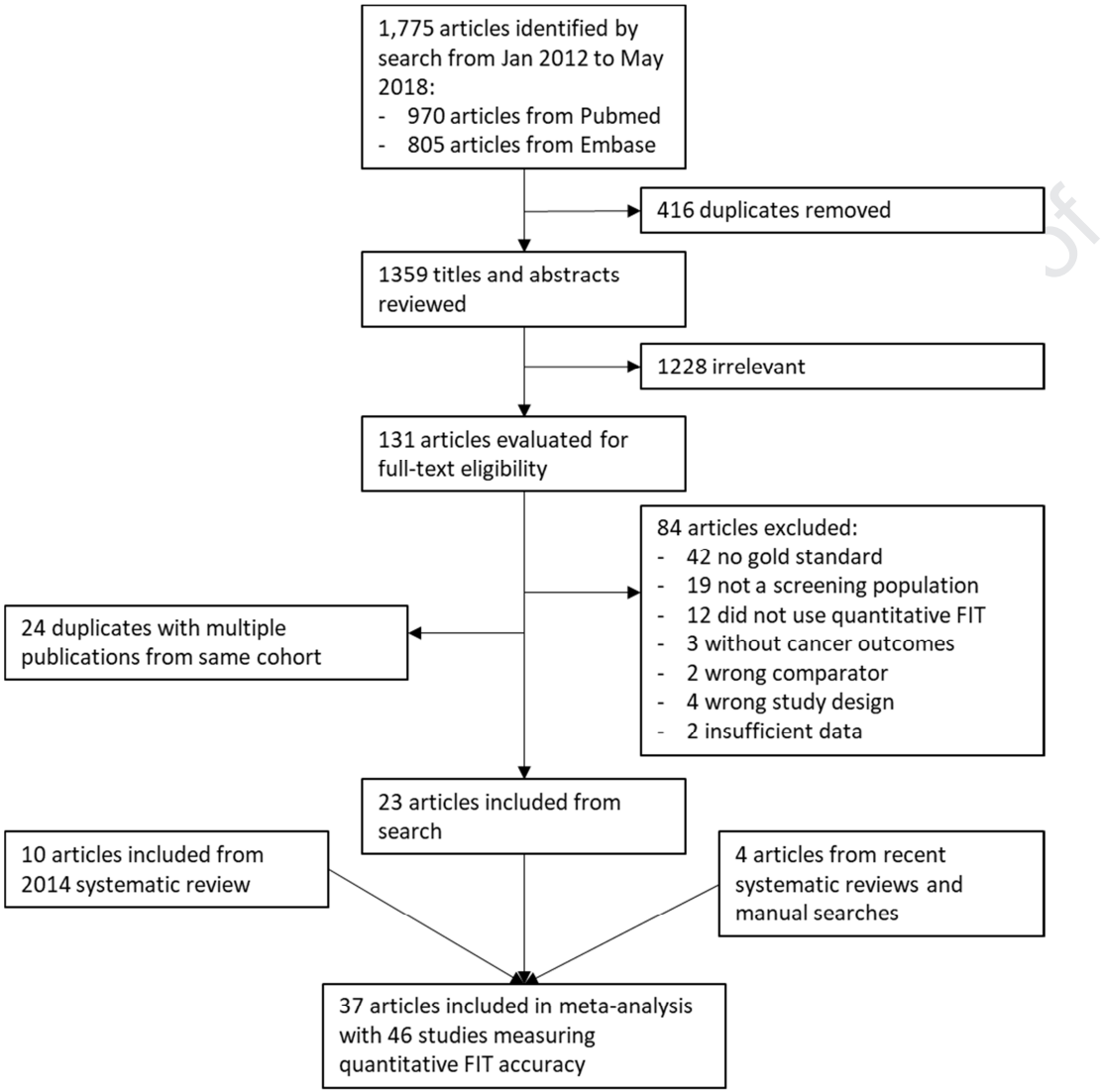


Table 4: Detailed information for included studies

#	Author, Year (Ref)	FIT Brand and details	Setting and Study Design	Reference/Gold Standard	Inclusion/Exclusion Criteria	Patient Characteristics	Prevalence of CRC, AN, AA	FIT Positivity Rate	CRC Sensitivity (95% CI)	CRC Specificity (95% CI)	AA definition	AA Sensitivity (95% CI)	CRC+AA Specificity (95% CI)	Comments and Applicability
1	Itoh, 1996	OC-Hemodia Cut-off: 10 µg/g 1 sample	Japan Asymptomatic patients 40 or older who worked for corporations participating in colorectal screening program were invited during 1991-1992. Diagnostic cohort design Enrollment order: consecutive Dates of recruitment: 1991-1992	Colonoscopy for FIT-positive patients and 2-year follow-up for FIT-negative patients FIT-negative patients were followed through health insurance claims and re-screened at 2 years. All treated cases, regardless of site for treatment, could be identified because all medical expenses are incurred by a single health insurance organization Blinding: Endoscopists were not blinded to the FIT results Interval between FIT and colonoscopy: Usually less than 2 months	Inclusion: Patients aged 40-59; employee of corporations that took part in CRC screening program Exclusion: symptoms of melena, hematochezia, diarrhea, relevant changes in stool frequency or abdominal pain. Prior colonoscopy within 5 years, family history for CRC, personal history of IBD or HNPCC	N: 27,860 Mean Age: 45.2 Age range: 40-59 years old Age <40: 0% Age >80: 0% Males: 86.1% (calc)	CRC 89/27860 0.3%	1490/27860 5.3%	77/89 86.5% (78-92)	26358/27771 94.9% (94.6-95.2)	Not included in analysis			OC-Hemodia has been discontinued and is no longer in production. Fairly young population as mean age is 45. Overall, population appears to be an asymptomatic, primary care population. Women are under-represented. Funding: NR Did not stratify by age or sex
2	Nakama, 2001	OC-Hemodia Cut-off: 10, 30, and 60 µg/g 4 samples	Japan Patients who participated in medical check-up for CRC between 04/90-03/99	Colonoscopy for all patients	Inclusion: Asymptomatic patients aged over 40 years who participated in a medical check-up for colorectal cancer between 04/90-03/99 Exclusion: not stated	N = 4260 Age: 40-49: 27.1% 50-59: 35.8% 60-69: 21.8% 70+: 15.2% Calculated mean: 57.2 Male: 46.5%	27/4260 0.6%	At 150 ng/ml: 175/4260 4.1%	22/27 81.5%	4080/4233 96.4%	Adenomatous polyp > 1 cm		4059/4204 96.6%	Including participants with a family history of CRC Funding: government Did not stratify by age or sex
3	Liu, 2003	OC-Hemodia	Taiwan	Colonoscopy on all	Exclusion: Patients	N = 1387	CRC 6/1387	31/1387	3/6 50%	1353/1381	Polyp > 1 cm	6/37	1322/1344	Exact number of

		Cut-off: presumably 20 µg/g Number of samples and cut-off not specified, only "per manufacturer's instructions"	One center Patients participated in medical check-up and agreed to get both colonoscopy and upper endoscopy Dates of recruitment: 12/97-11/99	patients	undergoing only unidirectional endoscopy [only colonoscopy]; gross gastrointestinal bleeding, anal-rectal bleeding or gross blood on digital examination, previous history of a known gastrointestinal bleeding lesion, gastrointestinal cancer, previous gastrointestinal surgery, inflammatory bowel disease, and premenopausal females with iron deficiency anemia.	Mean age: 46.2 +/- 12.1 years Male: 47%	0.43% AA 37/1387 2.7%	2.2%		98.0%		16.2%	98.4%	patients <40 unclear. Few details about performance of OC-Hemodia (i.e. blinding, etc.). Funding: NR Did not stratify by age or sex.
4	Morikawa, 2005	Magstream 1000/Hem Sp Cut-off: 67 µg/g Quantitative FIT (magnetic particle agglutination) 1-sample, FIT	Japan 22,666 asymptomatic pts were consecutively enrolled to perform 1 sample FIT and colonoscopy at Kameda General Hospital or Kameda Makuhari Clinic between 1983-20002. Diagnostic cohort study Enrollment order: consecutive Dates of recruitment: 1983-2002	Colonoscopy for all patients regardless of FIT results. Blinding: Endoscopists were blinded to the FIT results Interval between FIT and colonoscopy: less than 2 weeks, participants brought the collection tubes on the day of colonoscopy and the stool samples were sent to the lab within 24 hours and tested immediately	Inclusion: Asymptomatic patients that voluntarily agreed to FIT and colonoscopy for CRC screening Exclusion: Patients who reported symptoms of disease of the lower GI tract including visible rectal bleeding, recent change in bowel habits, or lower abdominal pain that normally would require a medical evaluation. Pts lacking sufficient info on the polypoid lesion were also excluded.	After exclusion: N = 21,805 Mean age: 48.2 +/- 9.3 years Age <40: 18.8% Age >80: 0.07% Male: 72%	CRC 79/21805 0.4% AA 648/21805 3.0%	1231/21805 5.6%	52/79 65.8% (55-76)	20547/21726 94.6% (94.3-94.9)	Advanced colonic neoplasia was defined as adenomas 10 mm or more in diameter, adenomas with high-grade dysplasia, or invasive cancer. Therefore AA = AN – CRC	145/648 22%	20044/21078 95.1%	Magstream HemSp is not FDA approved and is not available in the US. However, it is available in Australia and several other countries. Fairly young population as 19% is <40 years of age.. Overall, population appears to be an asymptomatic, primary care population. Funding: NR Did not stratify by age or sex
5	Launoy, 2005	Magstream 1000/HemSp Cut-off: 67 µg/g 2 samples with >= 1 above 67 µg/g	France Patients aged 50-74 yrs attending a regular consultation	Colonoscopy for FIT-positive patients and 2-year follow-up for FIT-negative patients.	Inclusion: Patients aged 50-74 years old who were seeing their primary care physician Exclusion:	N: 7421 Mean age: 61.3 +/- 0.8 years Age range: 50-	CRC 28/7421 0.38%	434/7421 5.8%	24/28 85.7% (69-94)	6983/7395 94.5% (93.9-95.0)	Not included in analysis			Magstream HemSp is not FDA approved and is not available in the US. However, it is available in

		considered positive	with their physician were invited to participate. Diagnostic cohort design Enrollment order: consecutive Dates of recruitment: 1/01-12/02	FIT-negative patients were followed through a cancer registry. Only followed up 5597/6987 (80.1%) for 2 years, so not a complete 2-year cancer registry follow-up. Blinding: Endoscopists were not blinded to the FIT results. Interval between FIT and colonoscopy: NR	symptomatic patients and patients who were not average-risk	74 years old Age: 50-54 20.9% 55-59 20.3% 60-64 19.8% 65-69 22.1% 70-74 26.8% Males: 43%								Australia and several other countries. Overall, population appears to be an asymptomatic, average-risk primary care population. Funding: Caisse Nationale d’Assurance Maladie; Direction generale de la Sante; and Ligue contre le Cancer. FIT kits were supplied by the manufacturer Did not stratify by age or sex.
6	Sohn, 2005	OC-Hemodia Cut-off: 20 µg/g Quantitative FIT (optical latex agglutination technique) 1-sample FIT No diet or medication restriction Sample method: wet	Korea 3794 asymptomatic average risk screenees, and 304 CRC pts admitted to the National Cancer Center, Korea were studied prospectively	Colonoscopy for all patients regardless of FIT results Blinding: NR	Inclusion: Asymptomatic, average risk screenees, and 304 CRC pts admitted to the National Cancer Center, Korea from 5/01-11/02 were studied prospectively Exclusion: Subjects with a previous colorectal pathology such as CRC, or polyps, and who had a family history of FAP, HNPCC. Subjects with recent colorectal symptoms such as abdominal pain, diarrhea, constipation, and hematochezia. Also excluded failed colonoscopic exam or poor prep.	N = 3794 (screenee group) Mean age: 48.9 Age range 15-78 years old Age <40: 18.2% Age >80: 0% Male: 56.7%	CRC 12/3794 0.3% AA 67/3794 1.8%	1.4%	3/12 25% (8.9-53.2)	3732/3782 98.7% (98.3-99.0)	High-risk adenomas were defined as adenomas with high grade dysplasia, a 10 mm or greater diameter or with at least 25% villous components.	4/67 6% (2-15)	3678/3727 99% (98-99)	OC-Hemodia has been discontinued and is no longer in production. Fairly young population as 18% is <40 years of age. Overall, population appears to be an asymptomatic, primary care population. Funding: NR Not stratified by age or sex
7	Nakazato, 2006	OC-Hemodia Cut-off: 16 µg/g	Japan	Colonoscopy for all patients	Inclusion: Asymptomatic adults	N = 3090	CRC 19/3,090 0.6%	404/3090 13.1%	10/19 52.6%	2677/3071 87.2% (86.0-	Large adenoma > 10	13/53 25% (13-	2637/3018 87%	OC-Hemodia has been

		Two sample with >1 of 2 samples with 16 µg/g considered a positive test	Cross-sectional analysis of asymptomatic adults who underwent a colonoscopy and a FIT in a single day Diagnostic cohort design Enrollment order: consecutive Dates of recruitment: 7/98-7/02	regardless of FIT results Blinding: Endoscopists were blinded to the FIT results Interval between FIT and colonoscopy: Less than 1 month, but majority within 1 week	willing to undergo both a colonoscopy and FIT Exclusion: Personal history of CRC and colonoscopic treatment of colorectal neoplasm, history of altered bowel habits, rectal bleeding, IBD, FAP, HNPCC	Mean age: 53.4 +/- 8.2 years Age range: 25-81 years old Age <40: 3.0% Age >80: 0.06% Male: 85%	AA 53/3,090 1.7%		(30.1-75.1)	88.4)	mm	36)		discontinued and is no longer in production. Fairly young population as 3% is <40 years of age. Overall, population appears to be an asymptomatic, primary care population. Funding: NR Did not stratify by age or sex
8	Levi, 2007	OC-Micro Cut-off: 15 µg/g 3 samples >= 1 of 3 samples with >= 15 µg/g considered a positive result 3 day collection, no restrictions	Israel 1000 consecutive ambulatory patients, some asymptomatic but at increased risk for CRC and some symptomatic. We only analyzed a subset of 80 asymptomatic patients with a family history of CRC. Asymptomatic, above average-risk due to family history of CRC. Prospective, cross-sectional study design Enrollment order: consecutive Dates of recruitment: NR	Colonoscopy for all patients regardless of FIT results. Blinding: Endoscopists were blinded to the FIT results Interval between FIT and colonoscopy: FIT samples were prepared one week prior to the colonoscopy	Inclusion: Referred for colonoscopy Exclusion: Concurrent hospitalization; visible rectal bleeding; IBD; hematuria; menstruation at time of stool specimen; inability to prepare FIT	N: 1000 Analyzing subset with family history (N = 80) Age: NR for subgroup Age range: NR Age <40: NR Age >80: NR Male: NR for subgroup	CRC 3/80 3.8% AA 15/80 18.8%	15/80 18.8%	2/3 66.7% (21-94)	64/77 83% (73-90)	>= 10 mm, villous histology, any high-grade dysplasia	8/15 53.3%	57/62 91.9%	OC-Micro is FDA approved and available in the US. It has been replaced by OC-Sensor. In addition, age was not reported in this subgroup and 100% of sample had a family history of CRC. Overall, population appears to be asymptomatic with slightly above average-risk primary care population. Funding: Eiken Chemical provided the instruments, reagents, and partial financial support for administration. Foundation grant. Did not stratify by age or sex

9	Castiglione, 2007	OC-Hemodia, developed with the OC-Sensor instrument Cut-off: 20 µg/g 1 sample	Italy Regional screening program 19 municipalities in the Province of Florence Dates of recruitment: 01/00-12/02 Follow-up with Tuscany Cancer Registry	Cancer registry follow-up to 2 years	Subjects aged 50-70, living in 19 municipalities in the Province of Florence, and attending FOBT screening from 01/00-12/02 were eligible for the present study.	N = 27503 tests (24913 individuals) Calculated mean: 58.1 Age 50-59: 50% Age 60-69: 47% Age 70: 3.3% Male: 47.8%	CRC 83/27503 0.3% AA 219/27503 0.8%	1097/27503 4.0%	67/83 80.7%	26390/ 27420 96.2%	Not included in analysis			Discrepancy between number of tests and number of individuals. Sens/spec based on number of tests Funding: NR Did not stratify by age or sex
10	Graser, 2009	FOB Gold assay Cut-off: 14 ng/ml, 2.38 µg/g Two 10ml stool sample containers FIT was performed in each of the two samples per patient	Germany Prospective colorectal cancer screening cohort study of average risk adults	Colonoscopy for all participants, augmented by Segmental unblinding (enhanced gold standard)	Inclusion: Participants had to be 50 years of age and free of symptoms of colonic diseases such as melenic stools, hematochezia, diarrhea, relevant changes in stool frequency or abdominal pain Exclusion: Prior OC within the last 5 years, and positive family history for CRC (one first-degree relative diagnosed with CRC before age 60 or two first-degree relatives diagnosed with CRC at any age). Persons with a history of or present IBD, hereditary colorectal cancer syndromes, a body weight 150 kg or severe cardiovascular or pulmonary disease were also excluded.	N = 285 (for FIT) Age range: 50-81 Mean age: 60.5 (SD 7.0) Male: 55%	In screening population: CRC 1/285 0.35% AA 24/285 8.4%	45/285 15.8%	1/1 100%	240/284 84.5%	>= 10 mm, villous histology, high-grade dysplasia	7/24 29.2%	223/260 85.5%	CRC results in detailed table Funding source: industry Did not stratify by age or sex
11	Park, 2010	OC-Micro Cut-off: 10 µg/g, 15 µg/g, 20 µg/g 1-, 2-, and 3-sample FIT	Korea 1020 consecutive asymptomatic, average risk people between	Colonoscopy for all patients regardless of FIT results. Blinding: Endoscopists were	Inclusion: Asymptomatic, average risk, age 50-75, who were undergoing a screening colonoscopy.	After exclusion: N = 770 Mean age: 59.3 +/- 7.5 years	At 20 µg/g CRC 13/770 1.7% AA 59/770 7.7%	86/770 11.2%	10/13, 76.9% (46.2-95.0)	709/757 93.7% (90-94)	>= 10 mm, villous histology, high-grade dysplasia	14/59 23.7% (14-37)	664/698 95.1% (93.3-96.6)	OC-Micro is FDA approved and available in the US. It has been replaced by OC-Sensor.

		>= 1 of 2 samples, or >= 1 of 3 samples with the specified threshold concentration considered positive	50-75 years of age undergoing screening colonoscopy from 4 tertiary medical centers in South Korea were invited to the study. Asymptomatic, average risk Prospective cohort design Enrollment order: consecutive Dates of recruitment: 12/07-11/08	blinded to the FIT results Interval between FIT and colonoscopy: Stool specimens from 3 daily or consecutive BMs were collected and applied on the FIT sampling probes during the week before colonoscopy	Exclusion: History of IBD, positive FOBT, polyps or CRC. History of colonoscopy or sigmoidoscopy within 5 years. Symptoms of lower GI issues, visible rectal bleeding, or a family history of CRC.	Age range: 50-75 years old Age <40: 0% Age >80: 0% Males: 51.4%								Overall, population appears to be an asymptomatic, average-risk primary care population. Funding: FIT kit, reagents, and research provided by Eiken Chemical. Did not stratify by age or sex
12	Levi, 2011	OC-Micro Cut-off: 14 µg/g 3 samples on consecutive days	Israel Average risk persons aged 50-75 years were offered either FIT or HO-SENSA according to a randomization program based on the SES of the primary care clinic. Patients from 9 primary care clinics of Clalit Health Services (CHS) in Tel Aviv Randomized prospective cohort design study All included people received an invitation letter to participate in the study.	Colonoscopy for FIT-positive patients and 2-year follow-up for FIT-negative patients. All the participants who performed the FIT, regardless of its results, were followed through the Israel National Cancer Registry Blinding: Endoscopists were not blinded to the FIT results Interval between FIT and colonoscopy: NR	Inclusion: Asymptomatic people aged 50-75 who received care at the 9 primary care clinics of CHS Exclusion: Patients who had undergone a colonoscopy or sigmoidoscopy in the last 5 years, patients who participated in gFOBT screening within 2 years, IBD history, CRC history	4,657 were randomized to FIT arm but only 1536 FIT kits were dispensed Of the 1536 kits dispensed, 1204 returned the FIT kits After exclusion: N = 1204 Mean age: FIT 60.4 +/- 7.6 years Age <40: 0% Age >80: 0% Male: 43.6%	CRC 6/1204 0.5% AA 29/1204 2.4%	153/1204 12.7%	6/6 100% (52-100)	1051/1198 87.7% (86-90)	>= 10 mm, villous histology, any high-grade dysplasia	Unable to calculate (no false negatives)		OC-Micro is FDA approved and available in the US. It has been replaced with OC-Sensor. Overall, population appears to be an asymptomatic, average-risk primary care population. Funding: Eiken Chemical provided the instruments, reagents, and partial financial support for administration. Did not stratify by age or sex

			Asymptomatic people willing to participate were instructed to go to the primary care clinic and ask for the FIT/FOBT kits. Enrollment order: random Dates of recruitment: NR											
13	Chen, 2011	OC-Sensor Cut-off 20 µg/g 1 sample Results for intervals (1-19, 20-39, 40-59, 60-79, 80-99, and > 100 ng/mL) also presented	Taiwan Participants part of a community-based colorectal screening program (part of larger multiple-screening program). 56025 individuals aged 40-69 identified from population registry in Keelung, Taiwan. Prospective cohort with staggered entry Dates of recruitment: 2001-2007	Colonoscopy recommended for positive tests. For those who did not do colonoscopy or had negative screen, linkage to the national cancer registry.	Inclusion: Unclear. Population invited to a screening program for residents aged 40-69. Number with family history of CRC not reported.	N = 45992 Mean age (calculated): 53 40-49 44% 50-59 32% 60-69 24% Male: 37%	CRC 115/46355 0.25% Only screen detected adenomas reported	2031/46355 4.4% (at 20 µg/g)	70/115 60.9%	44279/46240 96%	Adenomas larger than 10 mm were defined as advanced	Only screen detected adenomas reported		Numbers extracted those for the full follow-up (median 4.39 years, IRQ 2.53-6.12), which may artificially lower the sensitivity, especially in the setting of repeat screening. Other results presented in rates. May be worth contacting the study authors to obtain number of cancers within 1 or 2 years follow-up. Funding: No funding source Did not stratify by age or sex.
14	De Wijkerslooth, 2012	OC-Micro/Sensor Cut-off: 10, 15, 20 µg/g 1 sample	Netherlands Asymptomatic subjects who voluntarily underwent screening colonoscopy as part of a colon cancer screening program Enrollment	Colonoscopy for all patients regardless of FIT results Blinding: Endoscopists were blinded to the FIT results Interval between FIT and colonoscopy:	Inclusion: Asymptomatic individuals from Amsterdam and Rotterdam regions Exclusion: Invitees who had a prior colonoscopy, CT colonography, double contrast barium enema within 5 years, personal history of	After exclusion: N = 1256 Mean age: 60 Age range: 50-75 years Male: 51% Family history of CRC:	CC 8/1256 0.6% AA 113/1256 9%	71/1256 5.7% (at 20 µg/g)	6/8 75% (36-96)	1183/1248 95% (93-96)	>= 10 mm, villous histology, any high-grade dysplasia	33/113 29% (21-39)	1103/1137 97% (96-98)	OC-Micro/Sensor is FDA approved and available in the US. In addition, 15% of sample had a family history of CRC. Overall, population appears to be an asymptomatic, average-risk

			order: Randomized Prospective cohort design (part of COCOS-trial) Dates of recruitment: 6/09-7/10	Usually less than 48 hours	CRC, IBD, or adenomas, and individuals with an end stage and a life expectancy of less than 5 years	193/1256 15.4%								primary care population. Funding: The Netherlands Organization for Health Research and Development and by the Center for Transitional Molecular Medicine Did not stratify by age or sex
15	Wong, 2012	MagStream HemSp/HT (tube-based wet sampling, immunochemical test) Cut-off: 67 µg/g One sample for quantitative FIT 2 samples for qualitative FIT	Canada Regional cancer screening program Referred for elective screening colonoscopy Dates of recruitment: 4/08-10/09	Colonoscopy on all patients	Inclusion: Asymptomatic, 50-75 years of age, and no personal or family history of colorectal cancer or polyps. Participants at increased risk for colorectal cancer were included if they were 40-75 years of age with known personal or significant family history of colorectal cancer or polyps. Exclusion: Under 40 or over 75 years of age, unable to understand or sign the informed consent, or had a recent history of visible hematochezia or IBD. Participants with significant medical comorbidities were also excluded.	N = 1075 Mean age: 56.3 years Male: 46.25% 42% with first degree family hx of cancer, 12% of polyps	CRC 2/1075 0.2% Screen relevant neoplasia 69/1075 6.4%	94/1075 8.7% at 67 µg/g	2/2 100%	981/1073 91.4%	>10 mm diameter, tubulovillous or villous structure, and high-grade dysplasia	24/67 35.8%	938/1006 93.8%	Results provided by private communication Funding: Capital Health Authority, Edmonton, Alberta, Canada. Beckman Coulter Inc., USA provided Hemoccult ICT collection cards and test devices. Fujirebio Inc., Japan provided the Magstream HT. Reagents and support were provided by Fujirebio Diagnostics Inc., USA. Did not stratify by age or sex
16	Brenner, 2013	RIDASCREEN Haemoglobin Cut-off: 24.5 µg/g Adjusted thresholds for 3 different FIT tests to match	Germany Asymptomatic, average-risk subjects who underwent screening colonoscopy	Colonoscopy for all patients regardless of FIT results. Blinding: Endoscopists were blinded to the FIT results	Inclusion: Average risk patients ages 50-79 years who were willing to undergo a screening colonoscopy and were willing to perform an FOBT and provide stool prior to	After exclusion: N = 2235 Mean age: 62.7 years Age range: 50-79 years	CRC 15/2235 0.7% AA 207/2235 9.3%	112/2235 5%	9/15 60%	2118/2220 95.4%	>= 10 mm, villous histology, any high-grade dysplasia	43/207 20.8%	1954/2013 97.1%	RIDASCREEN is not FDA approved and not available in the US. Overall, population appears to be an

		positivity rate of gFOBT Quantitative FIT 1-sample FIT	Enrollment order: Consecutive Prospective cohort design	Interval between FIT and colonoscopy: average about 4 days	colonoscopy. Exclusion: visible rectal bleeding, previous +FOBT, IBD, prior colonoscopy, bad prep, stool sampling after colonoscopy, incomplete colonoscopy, pseudopolyps found on colonoscopy	Age <40: 0% Age >80: 0% Male: 49.2%								asymptomatic, average-risk primary care population. Funding: German Research Foundation and by a grant from the German Federal ministry of Education and Research. R-Biopharm AG provided FIT kits without charge. Did not stratify by age or sex
17		OC- Sensor Cut-off: 6.1 µg/g Adjusted thresholds for 3 different FIT tests to match positivity rate of gFOBT Quantitative FIT 1-sample FIT	Dates of recruitment: 2005-2009					112/2235 5%	11/15 73.3% (44.8-91.1)	2121/2220 95.5% (94.6-96.3)	>= 10 mm, villous histology, any high-grade dysplasia	46/207 22.2%	1960/2013 97.4%	
18	Shin, 2013	OC Sensor Cut-off: unspecified, presumably 20 µg/g 27.2% quantitative FIT Sample number unclear	Korea National Cancer Screening Program Dates of recruitment: 2004-2007	Cancer ascertainment by linkage to national cancer registry	Inclusion: Medical Aid recipients and NHI beneficiaries invited to participate in the NCSP, men and women aged 50 years and older, lower 30-50% income bracket Exclusion: 528 participants with missing screening results	N = 354014 FIT kits first round Age range: 50-59 48.9% 60-69 38% 70+ 13.1 Calculated mean age: 61.4 Men: 43.6%	CRC 839/354014 0.24% AAs not noted as from cancer registry	9665/ 354014 2.73% (2.68-2.77)	434/839 51.7 (48.3-55.2)	343915/ 353175 97.3% (97.3-97.4)	Not included in analysis			OC-Sensor was the most popular FIT, but not exclusive. Concern that not all quantitative FIT were OC-Sensor or at which threshold. Used results from first round of screening. Sensitivity calculated using sensitivity within 1 year (interval cancer was defined as a CRC cancer that was diagnosed outside a screening program within a year from the time of a negative screening in the NCSP). Funding: Grant-in-Aid for Cancer Research and Control from the National Cancer Center, Korea

														and a grant from the National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea.
19	Imperiale, 2014	OC FIT-CHEK Cut-off: 20 µg/g 1 sample	US and Canada Cross-sectional study at 90 sites in US and Canada, private-practice and academic settings Dates of recruitment: 06/11-11/12	Screening colonoscopy on all participants	Inclusion: Age 50-84 scheduled for screening colonoscopy Exclusion: personal history of colorectal neoplasia, digestive cancer, or IBD; had undergone colonoscopy within the previous 9 years or a barium enema, computed tomographic colonography, or sigmoidoscopy within the previous 5 years; had positive results on fecal blood testing within the previous 6 months; had undergone colorectal resection for any reason other than sigmoid diverticular; had overt rectal bleeding within the previous 30 days; had a personal or family history of colorectal cancer; had participated in any interventional clinical study within the previous 30 days; or were unable or unwilling to provide written informed consent	N = 9989 Mean age: 64.2 (SD 8.41) Age range: 50-84 years Male: 46.3%	CRC 65/9989 0.65% High-grade dysplasia 39/9989 0.39% Advanced precancerous lesions 757/9989 7.6%	6.96% (taken from table extrapolated to 10,000 people)	48/65 73.8% (61.5-84.0)	9294/9924 93.6% (proportion with negative test among those without cancer)	High-grade dysplasia or with > 25% villous histologic features or measuring > 1 cm in the greatest dimension	180/757 23.8%	8695/9167 94.9%	The study author definition of specificity: "with advanced precancerous lesions on colonoscopy excluded and only non-advanced adenomas and negative results include (the primary measure of specificity) and with only negative results included (the secondary measure of specificity). Had to back-calculate specificity among those without cancer, a s these numbers weren't presented. Funding: Exact Sciences Did not stratify by age or sex
20	Hernandez, 2014	OC-Sensor Cut-off: 10, 15, 20, 25, 30, 40 µg/g	Spain Multicenter, prospective, blinded cohort	Colonoscopy on all patients	Inclusion: asymptomatic men and women aged 50-69 years included in COLONPREV study	N = 779 Mean age 57.55 +/- 4.55 Male: 50%	CRC 5/779 0.6% AA 92/779 11.7%	FIT1 at 20 µg/g 55/779 7.1%	5/5 100% (90-100)	724/774 94% (92-95)	High-grade dysplasia or with > 25% villous histologic	26/92 28.3%	655/682 96%	Funding: government Did not stratify by age or sex

		2 samples on consecutive days. Only 1 sample results used.	study 3 hospitals in Spain, COLONPREV study in Galicia and Euskadi. Colonoscopy arm of a randomized trial comparing FIT and colonoscopy. Dates of recruitment: 1/10-6-11		Exclusion: Personal history of CRC, adenoma or IBD, family history of hereditary or familial CRC (i.e. >2 first-degree relatives with CRC or one diagnosed before the age of 60 years), severe comorbidity, previous colectomy, FIT screening in the past 2 years, sigmoidoscopy or colonoscopy within the past 5 years or symptoms requiring additional workup. Individuals were also excluded if they did not accept the study or refused to undergo the colonoscopy.						features or measuring > 1 cm in the greatest dimension			
21	Johnson, 2014	OC FIT-CHEK Cut-off: 20 µg/g 1 sample	United States Prospective cohort evaluation 61 sites Dates of recruitment: 3/12-11/12	Colonoscopy on all patients	Inclusion: Undergoing screening colonoscopy Exclusion: History of CRC or recommendation for repeat colonoscopy interval <10 years; neoadjuvant treatment; family history; IBD; acute or chronic gastritis; current cancer diagnosis other than CRC; overt bleeding or bleeding hemorrhoids; known infection with HIV, HBV, or HCV; IV fluids at time of sample collection. Patients with 'curative biopsy' at time of colonoscopy also excluded.	N = 193 in screening cohort Age range 50-59 64% 60-69 25% >69 11% Calculated mean age: 59.7 Male: 38%	CRC 2/193 1.0% AA 25/193 13%	6/193 3.1%	2/2 100%	187/191 97.9%	>10 mm diameter, tubulovillous or villous structure, and high-grade dysplasia	1/25 0.4%	163/166 98.2%	Results provided by private communication Funding: The study was sponsored by Epigenomics AG (Berlin, Germany). Eastern VA Medical School, Rockford Gastroenterology Associates, Ltd., Digestive Health Specialists and Molecular Pathology Laboratory Network, Inc., provided support in the form of salaries. Did not stratify by age or sex
22	Symonds, 2015	OC Sensor Cut-off: 10 µg/g	Australia	Colonoscopy on all patients	Inclusion: Any adults (40-85 years of age)	N = 1381	CRC 66/1381 4.8%	309/1381 22.4%	52/66 78.8%	1058/1315 80.5%	Villous or serrated	80/189 42.3%	949/1126 84%	Elevated number of cancers,

		1 sample	Patients scheduled for colonoscopy. Part of study for screening blood test (methylated BCAT/IKZF1, Clinical Genomics) FIT within 2 weeks of colonoscopy		scheduled for colonoscopy for standard clinical indications were approached about volunteering. Subjects were excluded if the scheduled colonoscopy was canceled, if insufficient blood was drawn, or if FIT kits were returned to the processing lab >2 weeks after sample collection. Exclusion: Younger age groups were not included as they are considered to be at lower risk for developing CRC.	Median age: 60.7 (42.0-79.0) Male: 29.4%	AA 189/1381 13.7%				morphology, >= 10 mm, high-grade dysplasia, or more than two tubular adenomas			though appears to be a screening population. Data taken from two identical abstracts. Assumption made that “significant neoplasia” = CRC + AA. Funding: FIT for the studies were subsidized by Elken Chemical Co., Japan. Parts of the research were supported by a project grant from NHMRC Australia. Did not stratify by age or sex.
23	Stegeman, 2015	OC-Sensor Cut-off: 10 µg/g 3 rounds (this article focuses on third round, calculations focused on first round), 1 sample each time	Netherlands Dynamic cohort study Screening-naïve part of biennial FIT-based CRC screening program	FIT positive received colonoscopy (if no contraindications); interval cancers were detected by link to the Netherlands Cancer Registry	Inclusion: Randomly selected individuals between 50 and 75 years of age, living in the same postal code areas in Amsterdam region as those invited to rounds one and two, were invited to participate in this third round of biennial FIT screening (eligible invitees). Exclusion: Except for those who had moved out of the area, passed the upper age limit, or had tested positive in a previous screening round; institutionalized people; the invitation letter indicated that invitees with rectal blood loss and/or a change in bowel habits should not	N = 2871 in first round Mean age 59 (SD 6.8) Male: 51%	1st round CRC 12/2871 0.23%	1st round: 233/2871 8.1%	15/20 75%	2633/2851 92.4%	>= 10 mm, villous adenoma, high-grade dysplasia	N/A	N/A	2-year registry between FIT used for those with a negative FIT Funding: Government and industry

					participate in screening, but contact their general practitioner instead.									
24	Lee, 2015	Hemo Techt NS-Plus C system Cut off: 6.3, 19 µg/g 1 sample	Korea 1397 individuals who received annual physical check-up at the Gangnam branch of Korean Association of Health Promotion (KAHP) Dates of recruitment: 07/12-03/13	Colonoscopy on all patients	Inclusion: Individuals aged 50-76 years who received annual physical check-up at Gangnam branch of KAHP Exclusion: Personal history of CRC	N = 1397 Median age: 58 years Male: 47%	At 19 µg/g: 14/1397 1%	72/1397 5.1%	10/14 71.4%	1321/1383 95.5%	High-risk adenoma >3 or >1 cm diameter or villous in nature or showing high-grade dysplasia	3/7 42.9%	1325/1376 96.3%	Letter to the editor Funding source: NR Did not stratify by age or sex
25	Jensen, 2015	OC-FIT CHEK samples analyzed with OC SENSOR DIANA automatic analyzer Cut-off: 20 µg/g 1 sample	United States Retrospective longitudinal study 2 integrated health systems, first round mailing in 2007 or 2008 to ages 50-70, 1 year follow-up. Extraction of 1st round of screening	Cancer within 1 year from cancer registry. 7% of positives did colonoscopy.	Inclusion: Participants aged 50-70 years on the date an initial kit was mailed to them in 2007 or 2008 Exclusion: Patients were excluded if they had been enrolled in the health plan for less than 1 year before the round 1 FIT mail date (to allow for the recording of prior out-of-system endoscopy procedures). They were also excluded if they were mailed a kit but subsequently had sigmoidoscopy or colonoscopy, were diagnosed with CRC, died or terminated membership in the health plan before returning the initial FIT or within 1 year after their round 1 mail date if no FIT was returned.	N = 323349 Mean age: 58.5 years (SD 5.7) Men: 46.4%	CRC 645/323349 0.2%	16037/ 323349 5%	545/645 84.5%	307202/ 322704 95.2%				Used results first round of screening, with one year of follow-up in registry. Reported sensitivity to two years was programmatic results, unable to calculate corresponding specificity. Funding: government Did not stratify by age or sex
26	Chen, 2016	OC-Sensor Cut-off: 20 µg/g	Taiwan Standard	National cancer registry and National Death	Restricted to those 50 years and older for this extraction.	N = 513283 total	CRC 763/141045 0.54$	8583/ 141045 6.1%	712/763 93.3% (91.5-95.1)	132411/ 140282 94.4% (94.3-	Not included in analysis			Extraction restricted to those 50+.

		1 sample	medical screening program between 1994 and end of 2007	File	Otherwise not noted.	Age 50+: 28% Extraction restricted to those 50+, which included age: 50-59: 53% 60+: 47% Calculated mean age: 60 Male: 46%	AAs not noted as from cancer registry			94.5)				Inconsistencies in numbers between Table 1 and Table 2, possibly because of 1 year vs. longer follow-up Funding: government Stratified by age and sex (ages 20-49)
27	Kim, 2016	OC-Sensor DIANA Cut-off: 10, 15, 20 µg/g (20 is principal cut-off) 1 sample FIT test	Korea National Cancer Screening Program at Kangbuk Samsung Hospital Dates of recruitment: 6/13-5/15	Colonoscopy on all participants	Inclusion: All subjects participating in the NCSP who got colonoscopy, including 770/1532 with positive results and 3489/33015 with negative results. Exclusion: Previous history of CRC or colorectal surgery, IBD, incomplete colonoscopy, under age 50.	N = 3990, after exclusions Mean age: 64.3 Male: 54.2%	CRC 79/3990 2% AA 376/3990 9.4%	770/3990 19%	58/79 73.4% (62.3-82.7)	3230/3911 82.6% (81.4-83.8)	Adenoma >10 mm in diameter, with tubulovillous or villous structure, or with high-grade dysplasia (HGD).	145/386 38.6% (33.6-43.7)	3006/3566 84.3% (83.1-85.5)	Positive FIT over-represented in this study as those with positive FIT are more likely to get colonoscopy, unclear direction of bias with that. Funding: NR Did not stratify by age or sex
28	Chen, 2016	FOB Gold Cut-off: 17 µg/g, and thresholds with positivity of 5% or 10% 1 sample	Germany 20 gastroenterology practices in BLITZ study Stool samples either frozen prior, or stool directly in test tube. Dates of recruitment: 11/08-09/14	Colonoscopy on all patients	Inclusion: Undergoing screening colonoscopy Exclusion: History of CRC or IBD, colonoscopy in the preceeding 5 years, inadequate bowel preparation, incomplete colonoscopy (cecum not reached)	N = 3466 Mean age: 62 +/- 6.4 years Range: 50-79 years Male: 50%	CRC 29/3466 0.84% AA 354/3466 10%	370/3466 10.7%	23/29 96.6%	3095/3437 90%	Standard: > 1 cm, villous components or high-grade dysplasia	116/354 32.8%	2861/3083 92.8%	Funding: government Did not stratify by age or sex
29	Redwood, 2016	OC-Sensor Diana Cut-off: 20 µg/g 1 sample Sent by mail, processing done at Mayo clinic	USA, Alaska Asymptomatic persons with any degree of self-reported Alaska Native heritage who were 40 through 85 years	Colonoscopy on all patients	Excluded patients if they (1) had undergone invasive screening tests in the previous 4 years or surveillance (i.e. CRC or polyp follow-up) in the previous 2 years, (2) had a history of	N = 435 in the screening group Median age: 52 years (IQR 50-59 years) Female: 60%	CRC 4/424 0.94% AA 56/424 13.2%	34/424 8.0%	3/4 75%	389/420 92.6%	Standard	15/56 28.6%	349/364 95.9%	Funding: foundation and industry Included large proportion getting surveillance colonoscopy

			old, were scheduled for average-risk screening or surveillance colonoscopy		upper GI cancer, (3) had overt hematochezia in the previous month, or (4) had inflammatory bowel disease or known hereditary CRC syndromes (e.g. Lynch syndrome, familial adenomatous polyposis)									
30	Kim, 2017	OC-Sensor Cut-off: 20 µg/g 1 sample	Dates of recruitment: 2007-2013	Colonoscopy on all patients	Exclusion criteria were as follows: Poor bowel preparation (n = 2574), lack of an adequate biopsy (n = 144), a history of CRC or colorectal surgery (n = 190), a history of IBD (N = 74), diagnosed with ischemic or infectious colitis during this study (n = 13), and subjects <30 years (n = 755)	N = 26,316 Age range: 30-39 43% 40-49 40% 50+ 17% Calculated mean age 42.4 Fam Hx of CRC 4% Male: 72%	CRC 16/26316 0.06% AA 454/26316 1.7%	805/26316 3.1%	11/16 69%	25493/26302 97%	>10 mm diameter, tubulovillous or villous structure and high-grade dysplasia	88/454 19.3%	25130/ 25846 97.2%	Young population, therefore excluded from pooled prevalence Funding: NR Stratified by age (30-30, 40-40, and >= 50) but not by sex
31	Aniwan, 2017	OC-Sensor Cut-off: 5, 10, 20, 30, 40 µg/g Automated analyzer machine (OC-Sensor DIANA machine) 1 sample	Thailand Cross-sectional study Health promotion program at the 6 university hospitals across Thailand. Represents all regions	Colonoscopy on all patients	Inclusion: Asymptomatic participants, aged 50-75 years, health promotion program participants Exclusion: Prior colon examination (endoscopy/radiologic imaging), previous colonic resection, previous history of CRC, IBD, and family history of hereditary CRC such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (at least 1 first degree relative with CRC before 60 years or at least 2 first degree relatives with CRC). Participants who had a positive FOBT in the	N = 1479 Mean age: 60.4 +/- 7.2 Range: 50-75 years Male: 38.3% 254/1479 with 1st degree family hx of CRC	CRC 14/1479 0.9% AA 123/1479 8.3%	108/1479 7.3%	11/14 78.6% (49-95)	1368/1465 93.4% (92-95)	>= 10 mm, villous adenoma, high-grade dysplasia	20/123 16.2%	1266/1342 94.3% (92.9-95.5)	Present results for Advanced Neoplasia = CRC + AA. Presumably 123 AAs. Funding: Government, foundation and industry Does not stratify by age or sex.

					past year.									
32	Van der Vlugt, 2017	OC-Sensor and FOB-Gold Cut-off: 10 µg/g 1 sample in each round of testing	Netherlands Screening-naïve part of biennial FIT-based CRC screening program Dates of recruitment: 2006-2014	FIT positive received colonoscopy; FIT negative were re-invited for screening biennially CRC detected during screening and non-screening programs (FIT interval cancers, colonoscopy interval cancers) Linked to Netherlands Cancer Registry through 3/15	Inclusion: 50-74 years living in target areas; screening-naïve Exclusion: From consecutive rounds: Participants who moved out of the area, those who had passed the upper age limit, institutionalized people, those with an estimated life expectancy of less than 5 years, those unable to give informed consent, and those who had tested positive in a previous screening round and had undergone a colonoscopy. Individuals with a history of IBD or CRC were advised not to participate in CRC screening.	N = 18716 (participated in FIT test) Age range: 50-76 years Round 1: MW (5028, median age 59 (54-65), male 2485, 49%); SW (9623, median age 60 (55-66), male 4779, 50%) Round 2: MW (10198, median age 59 (54-65), male 4981, 49%); SW (8185, median age 61 (56-66), male 3962, 48%) Round 3: MW (10032, median age 60 (55-66), male 4901, 49%); SW (9586, median age 60 (54-65), male 4648, 49%) Round 4: MW (9517, median age 61 (57-67), male4618, 49%); SW (9774, median age 61 (56-67), male 4672, 48%)	CRC 116/18716 0.62%	2140/18716 11.4%	89/116 77%	16549/18600 89%	Not included in analysis			Funding: Netherlands Organization for Health Research and Development of the Dutch Ministry of Health Stratified by age and sex

33	Haug, 2017	OC-Sensor Micro Cut-off: 10 µg/g 1 sample Multiple threshold reported for alternative scenarios: 11, 14, 22, 36, 45, 50 ng/mL	Amsterdam Prospective study was a random selection of the general Dutch population between 50 and 75 years of age in Nijmegen, Amsterdam, and surrounding areas Ongoing population based CRC screening study that started in 2006	Occurrence of CRC was determined by record linkage with the Dutch Comprehensive Cancer Center Positive FIT50 received colonoscopy; patients with a negative colonoscopy were considered not to require FIT screening for 10 years	Inclusion: Demographic data of all individuals aged 50-74 years living in the southwest of The Netherlands were obtained from municipal population registers to identify the target population. This population was screening-naïve since there was no CRC screening programme at the time of recruitment for this study. Exclusion: History of CRC, IBD, an estimated life-expectancy of <5 years, a colonoscopy, sigmoidoscopy or double-contrast barium enema within the previous 3 years and inability to give consent. Subjects were no longer invited to subsequent rounds if they tested positive at a prior screening round, if they had become >75 years of age, if they had moved out of the region or had died.	N = 4253 Age range: 50-74 years Mean age (SD): 60.5 (6.6) Male: 48%	CRC 36/4523 0.795% AA 180/4253 3.98%	380/4523 8.4%	22/25 88%	4140/4498 92%				Funding: NR Did not stratify by age or sex

34	Shapiro, 2017	OC FIT-CHEK Cut-off: 20 µg/g 1 sample	USA Clinics in Minneapolis and Indianapolis metro areas Dates of recruitment: 05/11-07/14	Colonoscopy for all patients	Inclusion: Asymptomatic patients aged 50-75 years who were scheduled to have a colonoscopy for CRC screening Exclusion: Having colonoscopy due to bleeding or other symptoms, positive or abnormal flexible sigmoidoscopy, double-contrast barium enema, computed tomographic colonography or FOBT. Patients were alsoneligible if they had >1 episode of rectal bleeding in the past 6 months, a personal history of CRC or colorectal polyps, a positive FOBT in the past 12 months, a colonoscopy within the past 5 years, a prior colon resection or other colon/rectal surgery, a history of IBD, a personal or family history of familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer, were currently taking anticoagulant medication, or were not able to read English.	N = 1006 Age: 50-54 15.9% 55-59 22.6% 60-75 61.5% Mean average: 55.6 years Male: 45.5%	CRC 2/1006 0.2% AA 53/1006 5.3% AN 55/1006 5.4%	AN from OC Sensor at 20 µg/g: 3%	0/2 0%	917/945 97%	Standard	6/38 15.8%	282/291 96.9%	Including participants with a family history of CRC, and cancer screening history Funding: The Division of Cancer Prevention and Control, Centers for Disease Control and Prevention provided financial support for the study through a contract with Battelle Memorial Institute.
35	Gies, 2018	CAREprime Cut-off: 6.3 (primary), 7, 12, 15, 26 µg/g 1 sample	Southern Germany Prospective, cohort study conducted with 20 gastroenterology	Colonoscopy for all patients	Inclusion: Targeted selection of all eligible 216 cases with CRC or AA, and random selection of 300 participants without CRC and AA from about 1,600 eligibe	N = 516 Age range: 50-79 years Mean age: 63.2 years	CRC 16/516 3.1% AA 200/516 38.8% AN 216/516 41.8%	71/516 13.8%	13/16 81.3% (54-96)	442/500 88.4%	Standard	62/200 31% (25-38)	274/300 91.3%	Used a case-control design. Included all cancers from the Blitz cohort, as well as 200 advanced adenomas, then
36	Gies, 2018	Hb Elisa Cut-off: 2						103/500 20.6%	13/1681.3% (54-96)	410/500 81.9% (79-		87/200 43.5%	257/300 85.7% (81-	

		(primary), 5, 15, 29 µg/g 1 sample	practices in Southern Germany. Enriched with CRC cases recruited in another study. Dates of recruitment: 2005-2010		participants of screening colonoscopy, with stool samples provided in 60 mL collection containers Exclusion: Not between 50-79 years, IBD, personal history of CRC, adenoma or polyps; previous colonoscopy in previous 5 years; stool sampling not before colonoscopy; incomplete colonoscopy; incomplete bowel preparation	Male: 55.6%				85)		(37-51)	89)	completed with 300 from screening cohort; used stool samples that have been stored for several years Funding source: government, foundation and industry
37	Gies, 2018	OC Sensor Cut-off: 4, 7, 10 (primary), 15, 18 µg/g						33/516, 6.4%	11/16 68.8% (41-89)	478/500 95.6% (94-97)		36/200 18% (13-24)	293/300 97.7% (95-99)	
38	Gies, 2018	RIDASCREEN Hb Cut-off: 8 (primary), 12, 15, 30 µg/g						77/516 14.9%	13/16 81.3% (54-96)	436/500 87.2% (84-90)		72/200 36% (29-43	272/300 90.7% (87-94)	
39	Gies, 2018	FOB-Gold Cut-off: 2, 15, 17 (primary), 18, 53 µg/g						38/516 7.4%	1/16 68.8% (41-89)	473/500 94.5% (92-96)		36/200 18% (13-24)	289/300 96.3% (94-98)	
40	Gies, 2018	Eurolyser FOB test Cut-off: 2, 6, 8, 15, 21 µg/g						35/516 4.8%	10/16 62.5% (35-85)	475/500 86.7% (84-90)		39/200 19.5% (14-26)	291/300 97% (94-97)	
41	Gies, 2018	ImmoCare-C Cut-off: 6, 6. 25 (primary), 9, 15, 17, 37 µg/g						79/516 15.3%	13/16 81.3% (54-96)	434/500 86.8% (84-90)		70/200 35.2% (29/42)	270/300 90% (86-93)	
42	Gies, 2018	QuantOn Hem Cut-off: 3.7 (primary), 4, 10, 15, 18, 30 µg/g						102/516 19.8%	13/16 81.3% (54-96)	411/500 82.2% (79-85)		83/200 41.5% (35-49)	257/300 85.7% (81-89)	
43	Gies, 2018	QuikRead go iFOBT Cut-off: 15 (primary), 23 µg/g						36/516 7.0%	10/16 62.5% (35-85)	474/500 94.7% (93-97)		37/200 18.5% (13-25)	290/300 96.7% (94-98)	
44	Chen, 2018	OC-Sensor Cut-off: 20 µg/g 1 sample	Taiwan National screening program Follow-up with nationwide cancer registry from entry until end of 2009	Cancer registry follow-up to 2 years	Participants aged 50 to 69 years who attended biennial nationwide CRC screening program with FIT between Jan 1, 2004 and Dec 31, 2009. Only those completing OC-Sensor included.	N = 723,113 Average age (calculated): 59 years Male: 38%	CRC 2005/ 723113 0.277%	28390/ 723113 4.0%	1496/2005 74.6%	694214/ 721108 96.3%	N/A			Funding: government
45	Selby, 2018	OC-Sensor Diana Cut-off: 20 µg/g Sent by mail, 1 sample	USA, California Organized FIT-based mailed out-reach programs from Kaiser Northern and Southern California.	Cancer registry follow-up for 2 years	Individuals were eligible if they had a quantitative FIT result available between January 1, 2013 and December 31, 2014, irrespective of whether it was their first-ever FIT; were	N = 640,859 Average age (calculated): 61.5 years Female: 53%	CRC 1245/ 640859 0.19%	48561/ 640859 7.6%	925/1245 74.3%	591978/ 639614 92.6%	N/A			Used programmatic sensitivity, which is proportion with cancer who had a positive FIT at baseline or follow-up. Programmatic

			Retrospective cohort, using programmatic sens/spec. Those with quantitative FIT available 01/13-12/14, with two years follow-up in cancer registry		50-75 years of age; were at average risk for CRC (no personal history of CRC, total colectomy, or IBD); had been members of the health system for >2 years before the test result date, to capture prior endoscopy examinations or FIT; and were members for >2 years after the test result date or until their CRC diagnosis date if it was within 2 years.									specificity is proportion without cancer with all negative results. Funding: government
46	Liles, 2018	OC-Auto FIT Cut-off: 20 µg/g Two kits sent by mail, to be completed on separate days Only 1-sample results used	USA, Kaiser Permanente Northwest, HMO Members receiving referral for screening colonoscopy between 12/11-06/14	Colonoscopy on all patients	Exclusion: High-risk diagnosis, recent endoscopy, not medically indicated (dementia, nursing home, hospice), needs interpreter, opt out of study	N = 2771 Average age (calculated): 60.0 Female: 51% Family history: 5.2%	CRC 2/2771 0.072%	116/2771 4.2%	2/2, 100%	2655/2769, 95.9%	Standard (currently + cancers)	28/209, 13.4%	2473/2560 96.6%	Author provided results for cancer sensitivity and specificity Funding source: government, Polymedco supplied test kits and analyzer Did not stratify by age or sex

Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

Figure 2: QUADAS-2 overview of study quality for included studies/cohorts

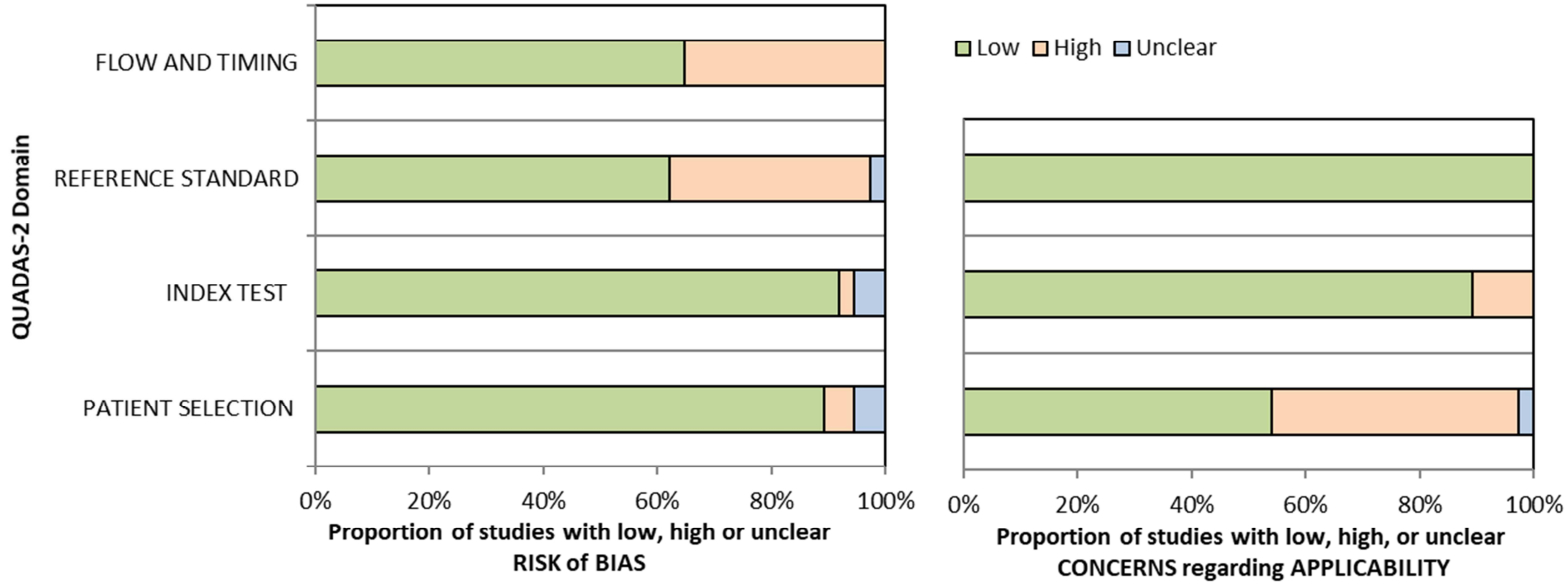


Table 5: Detailed QUADAS assessment for individual studies

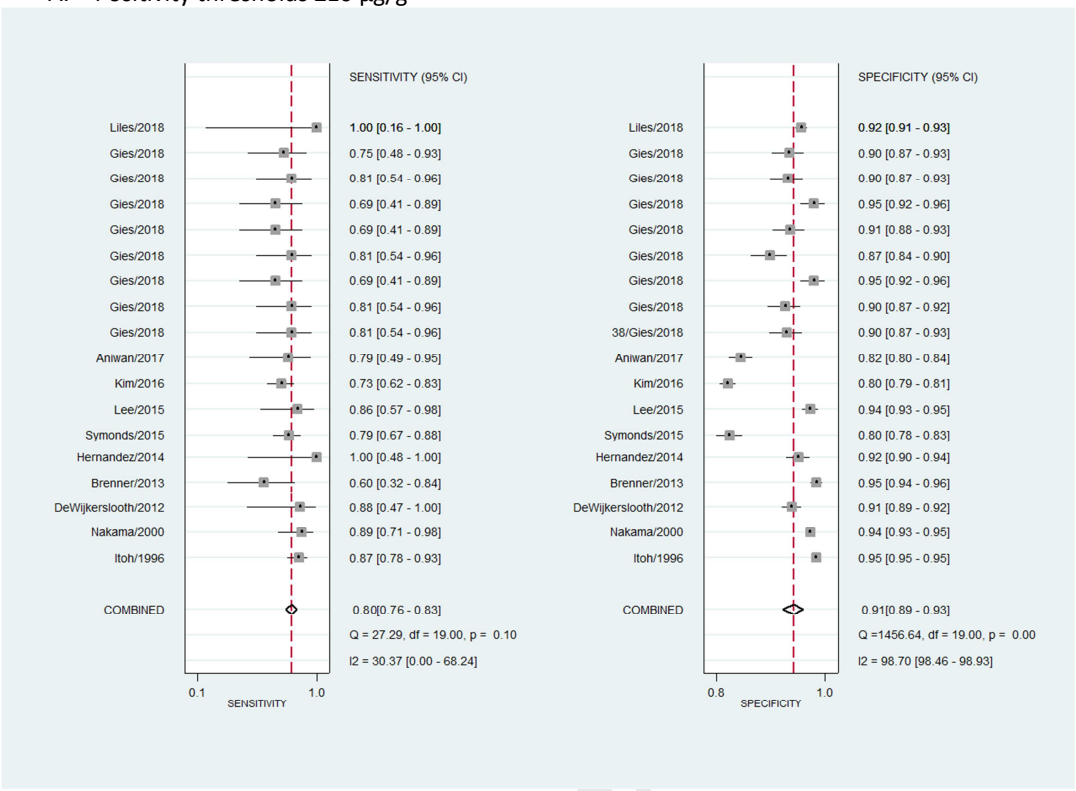
Author, Year (Reference)	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Itoh, 1996	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Nakama, 2001	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Liu, 2003	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Morikawa, 2005	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Launoy, 2005	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Sohn, 2005	Low risk	Unclear risk	Unclear risk	Low risk	High risk	High risk	Low risk
Nakazato, 2006	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Levi, 2007	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Castiglione, 2007	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Graser, 2009	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Park, 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Levi, 2011	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Chen, 2011	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
DeWijkersloot, 2012	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Wong, 2012	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Brenner and Tao, 2013	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Shin, 2013	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Imperiale, 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hernandez, 2014	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Johnson, 2014	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Symonds, 2015	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Stegeman, 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Lee, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jensen, 2016	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Chen, 2016	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Kim, 2016	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Chen and Warner, 2016	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Redwood, 2016	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Kim, 2017	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Aniwan, 2017	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Van der Vlugt, 2017	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Haug, 2017	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Shapiro, 2017	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk

Gies, 2018	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Chen, 2018	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Selby, 2018	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Liles, 2018	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk

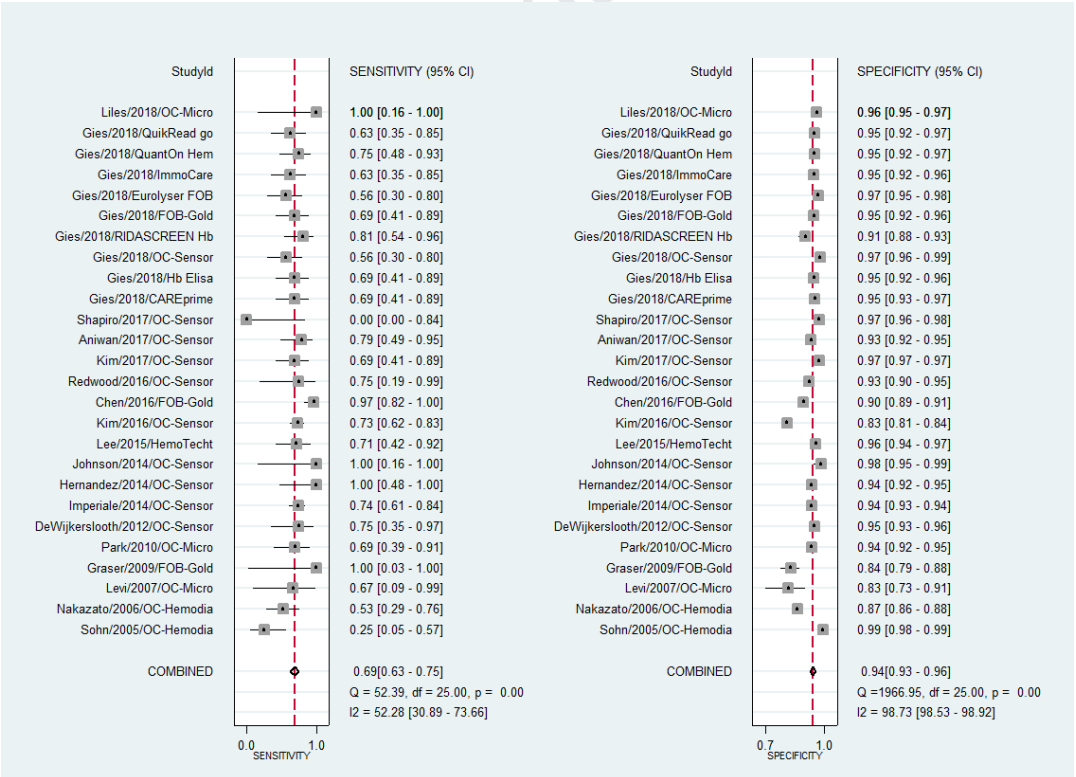
Supplemental materials for "Accuracy of the Quantitative Fecal Immunochemical Test…"

Figures 3A-D: Colorectal cancer detection at varying quantitative thresholds using all available positivity thresholds, from studies with colonoscopy follow-up

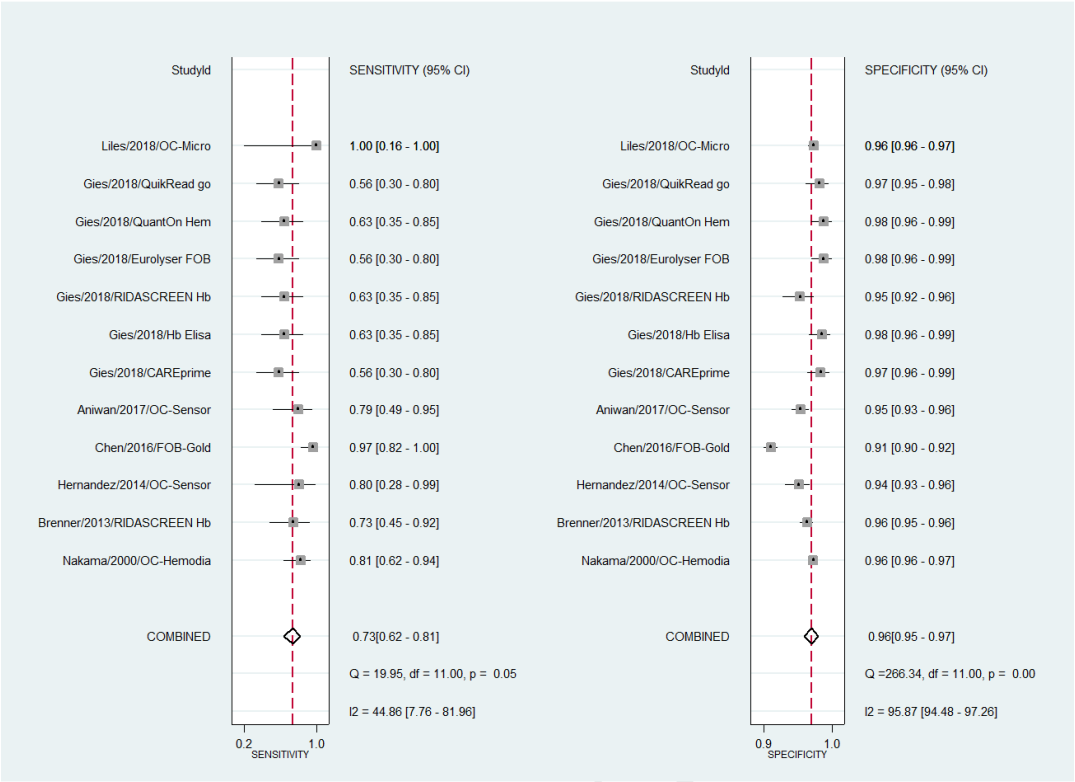
A. Positivity thresholds ≤10 µg/g



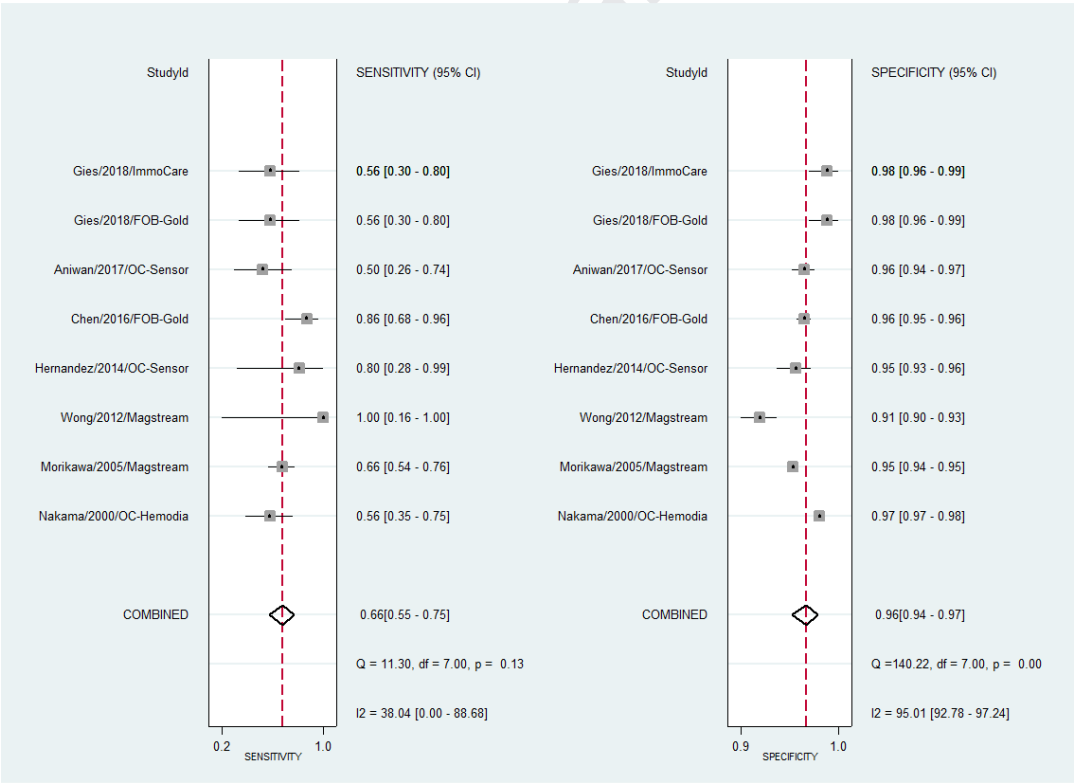
B. Positivity thresholds >10 and ≤20 µg/g



C. Positivity thresholds >20 and ≤30 µg/g



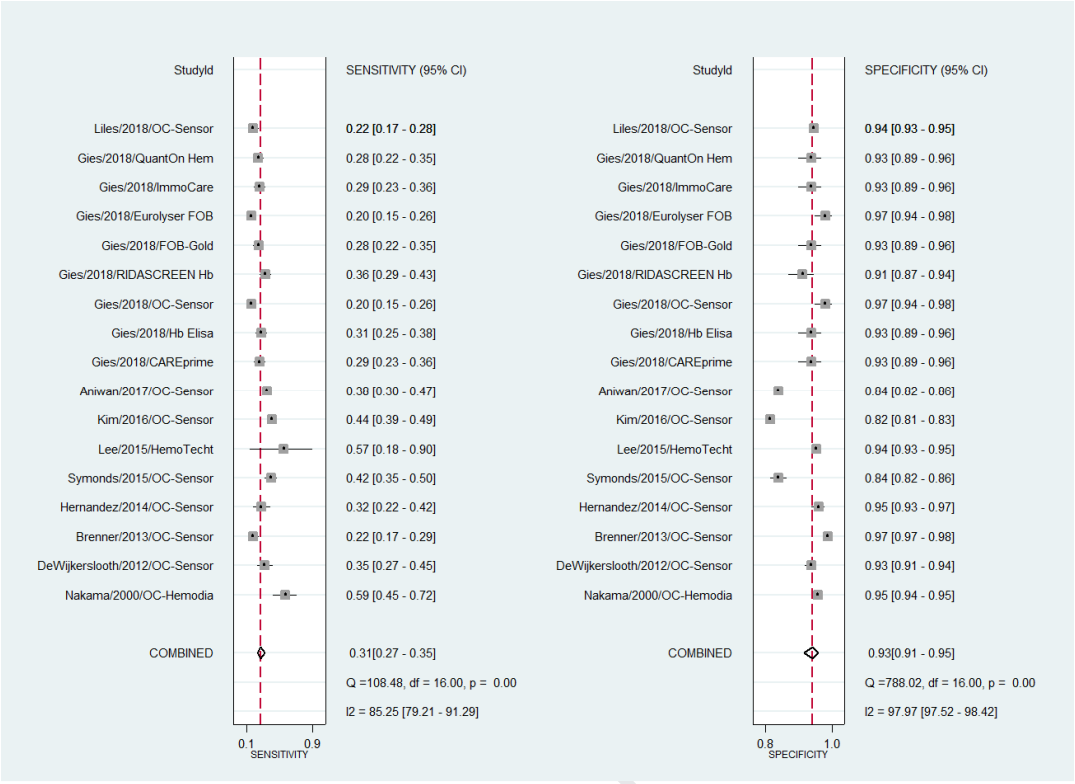
D. Positivity thresholds >30 µg/g



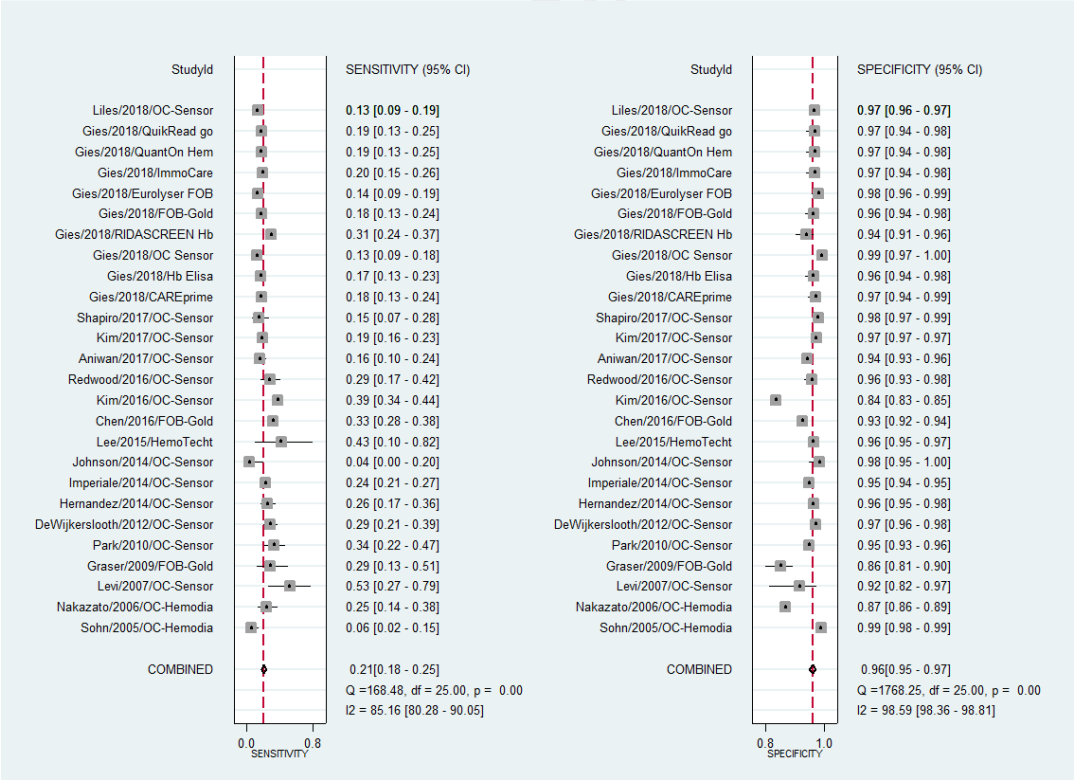
Supplemental materials for "Accuracy of the Quantitative Fecal Immunochemical Test…"

Figures 4A-D: Advanced adenoma detection at varying quantitative thresholds using all available positivity thresholds, from studies with colonoscopy follow-up

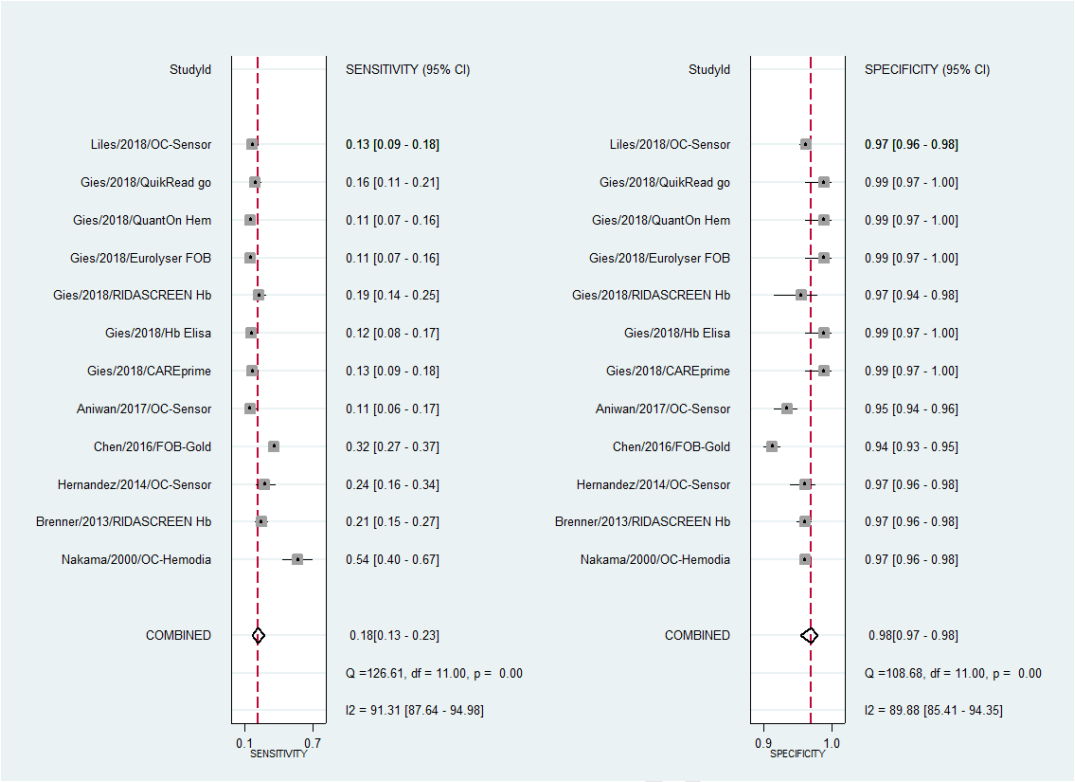
A. Positivity thresholds ≤10 µg/g



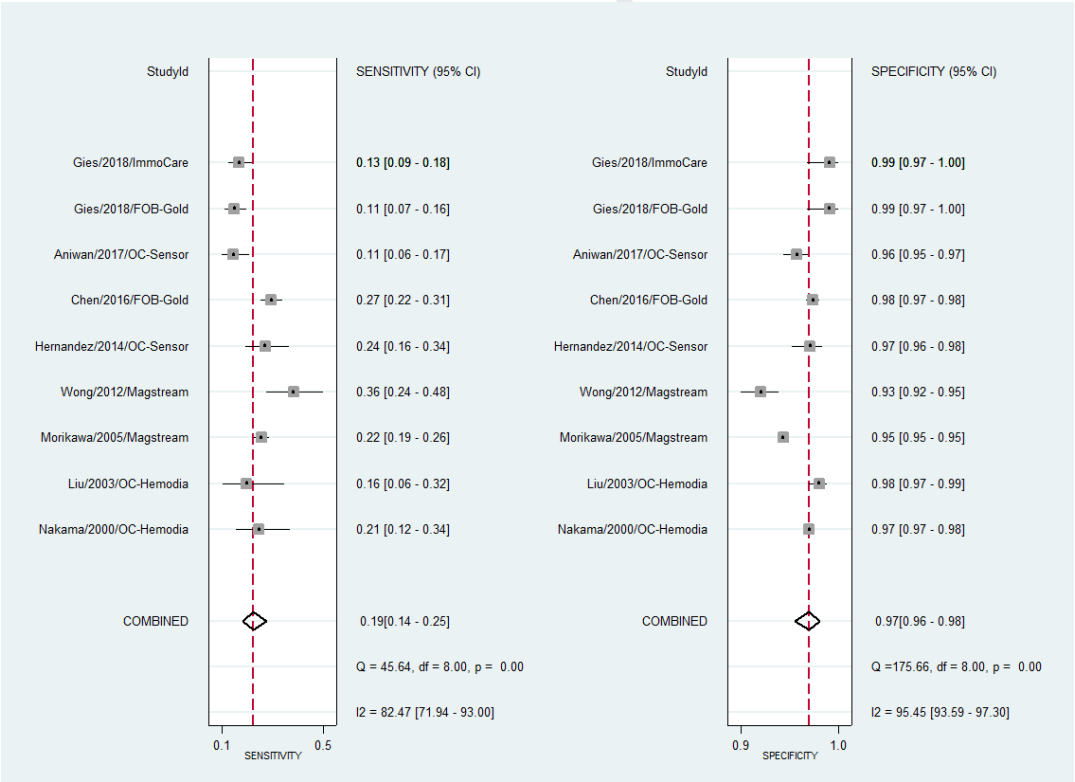
B. Positivity thresholds >10 and ≤20 µg/g



C. Positivity thresholds >20 and ≤30 µg/g

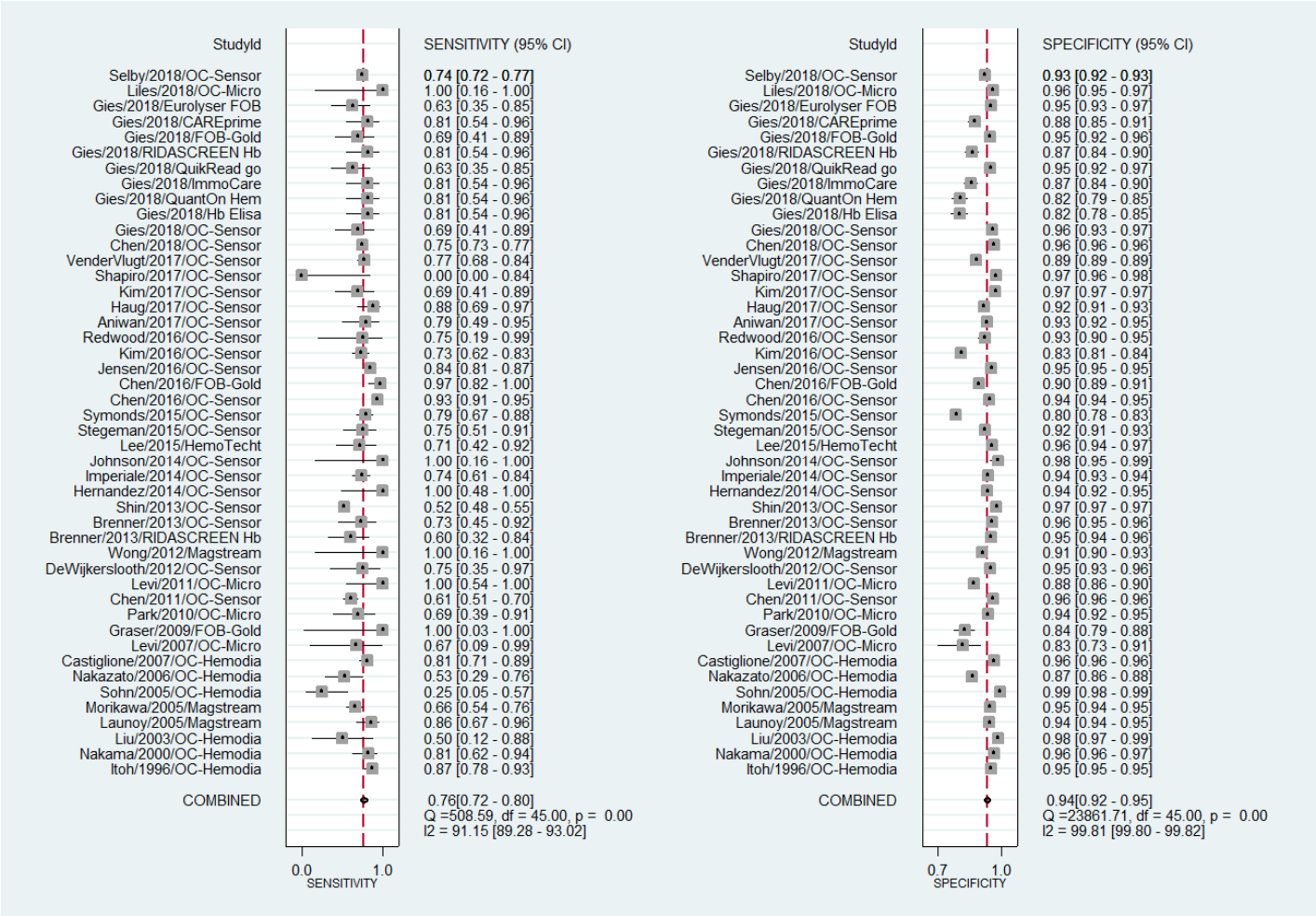


D. Positivity thresholds >30 µg/g



Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

Figure 5: Colorectal cancer detection, using the primary positivity threshold from all included studies



Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

Figure 6: Summary receiver operating characteristic for colorectal cancer detection, using the primary positivity threshold of all included studies

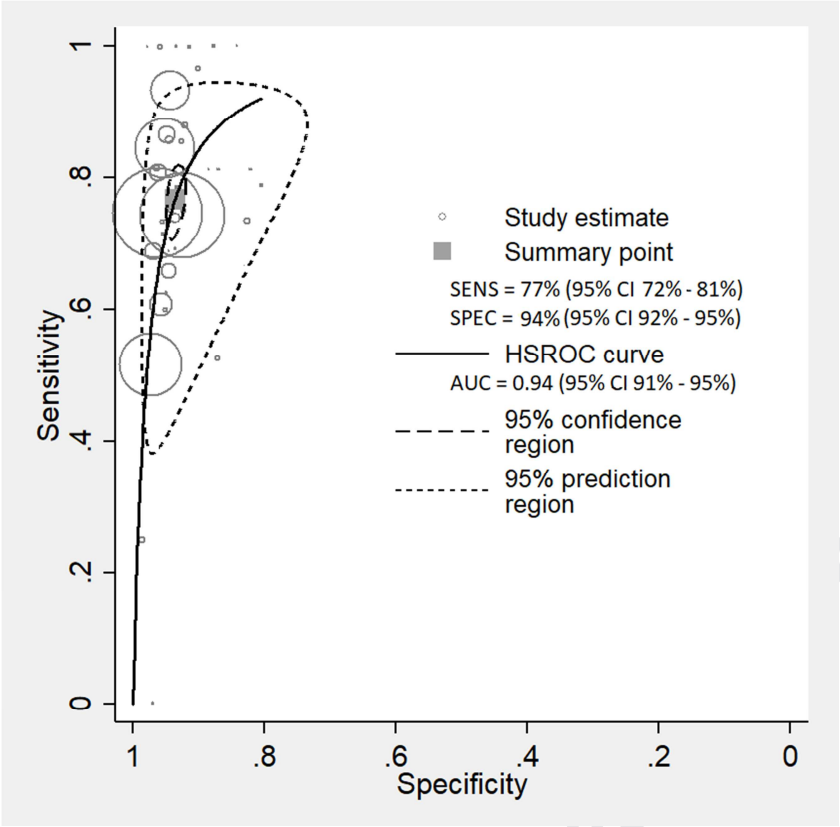
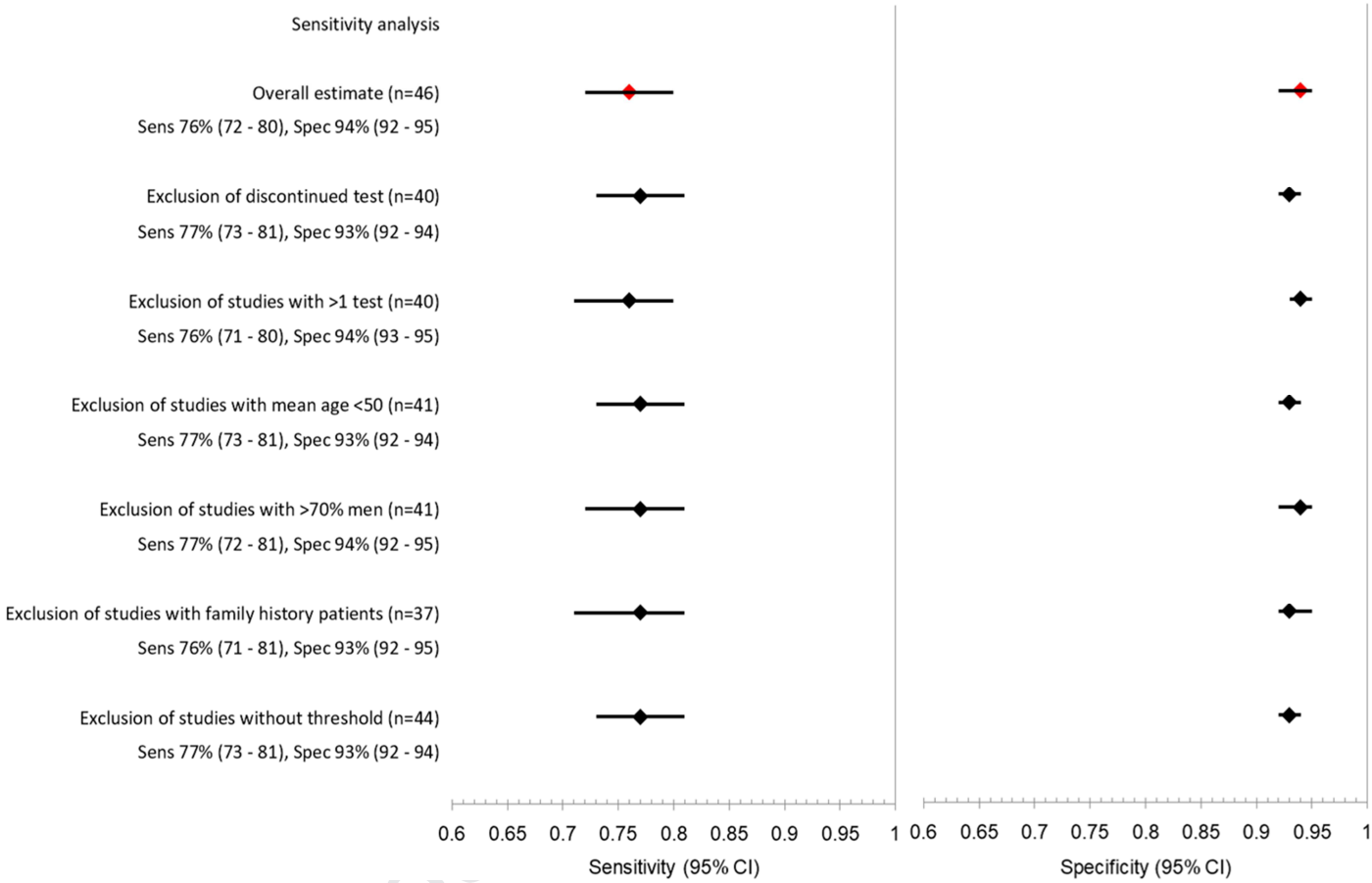
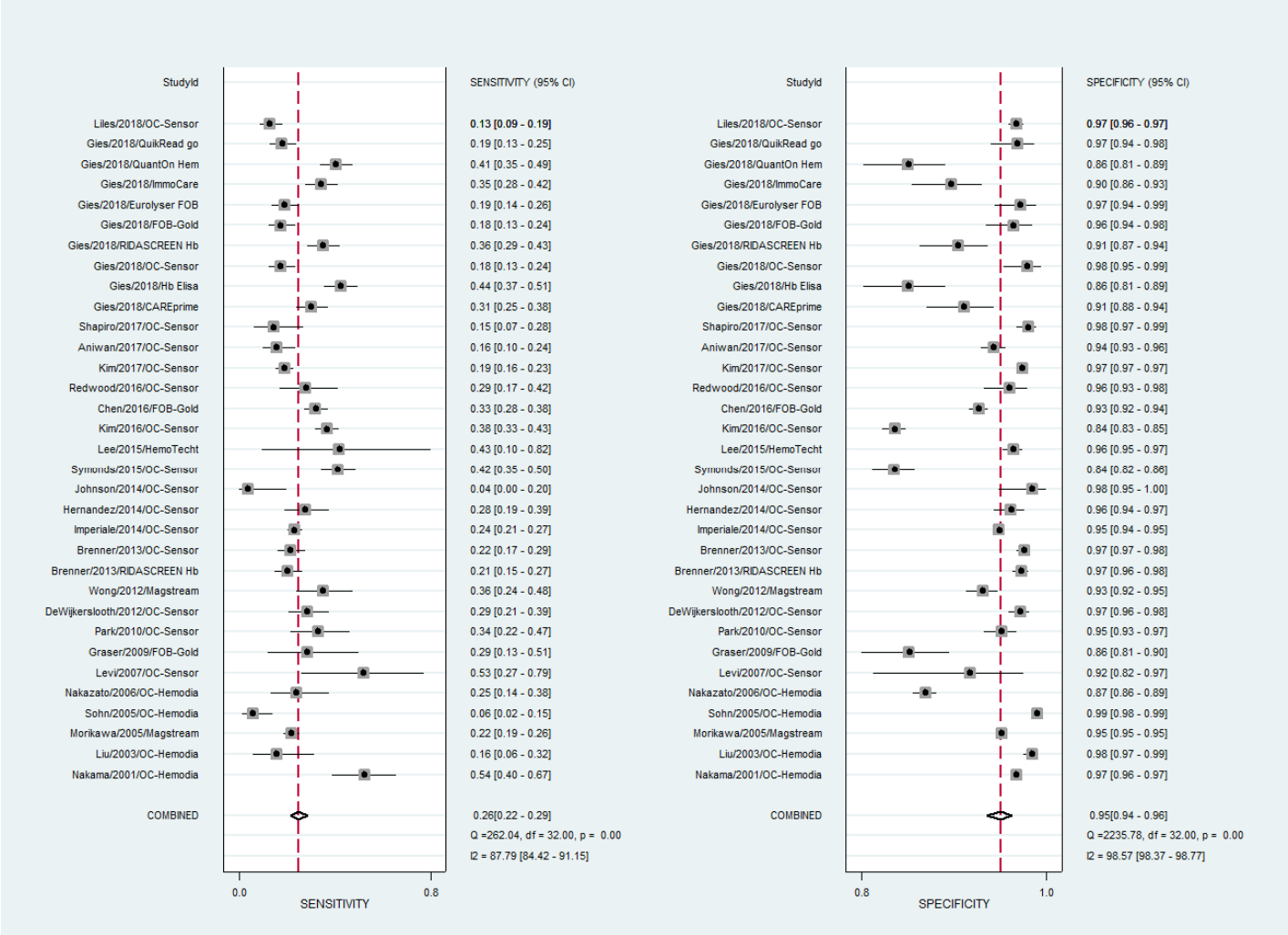


Figure 7: Sensitivity analyses for sensitivity and specificity of FIT for colorectal cancer detection including all studies, based on exclusion of select studies



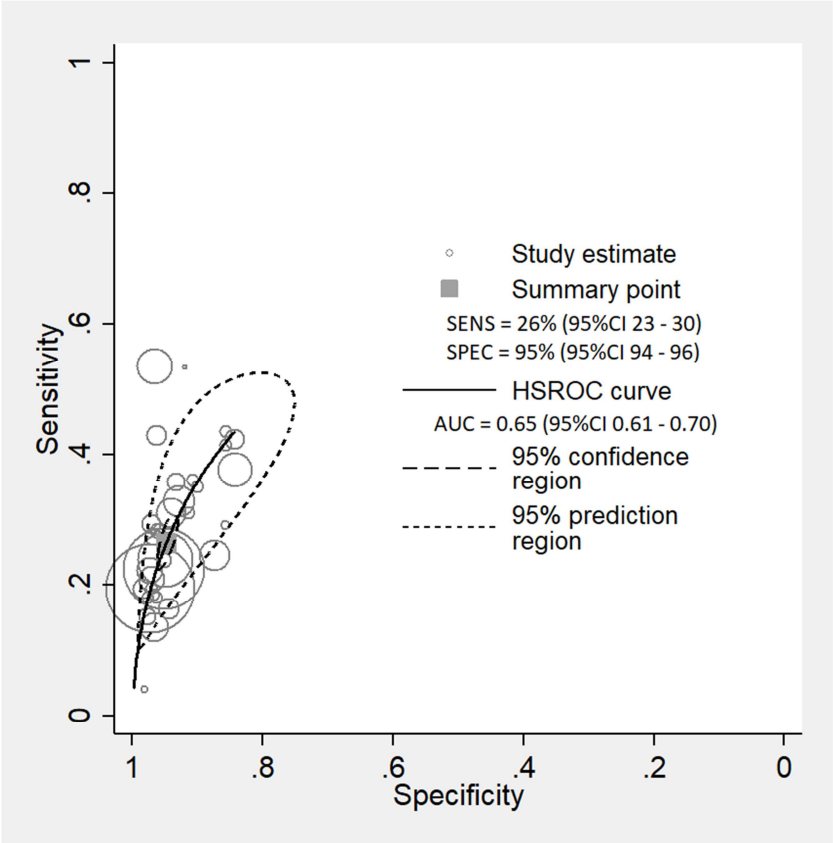
Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

Figure 8: Advanced adenoma detection, using the primary positivity threshold of all studies reporting sensitivity and specificity for advanced adenomas



Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

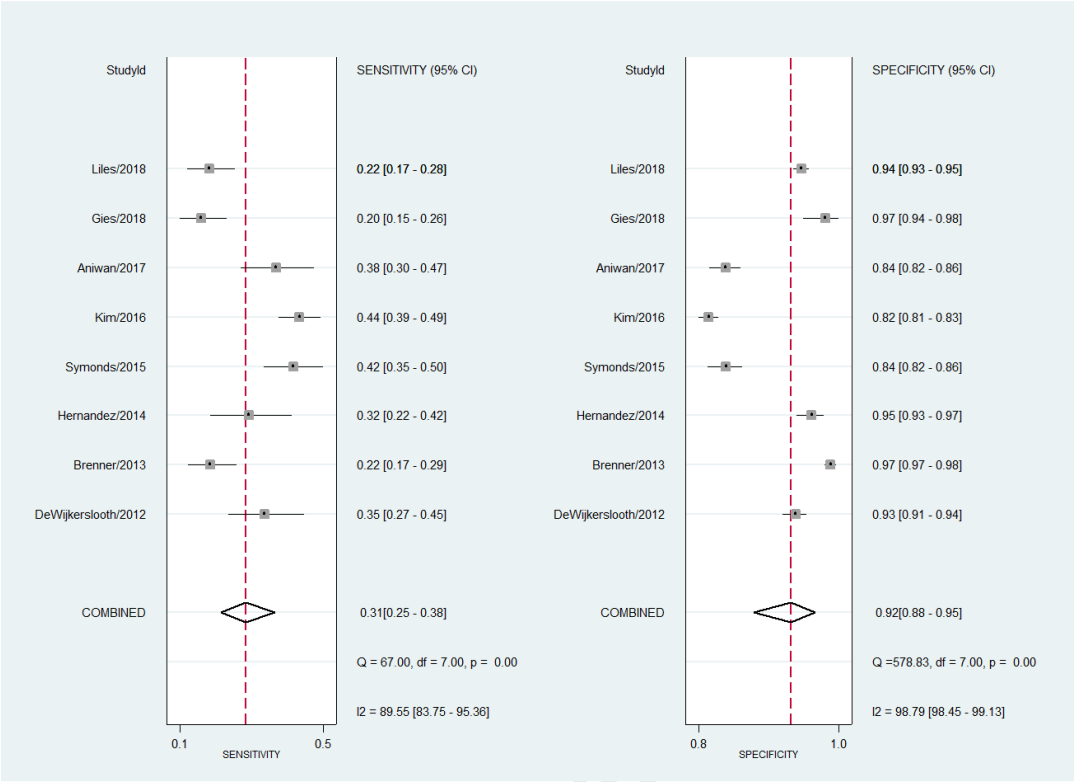
Figure 9: Summary receiver operating characteristic curve for advanced adenoma detection, using the primary positivity threshold of all included studies



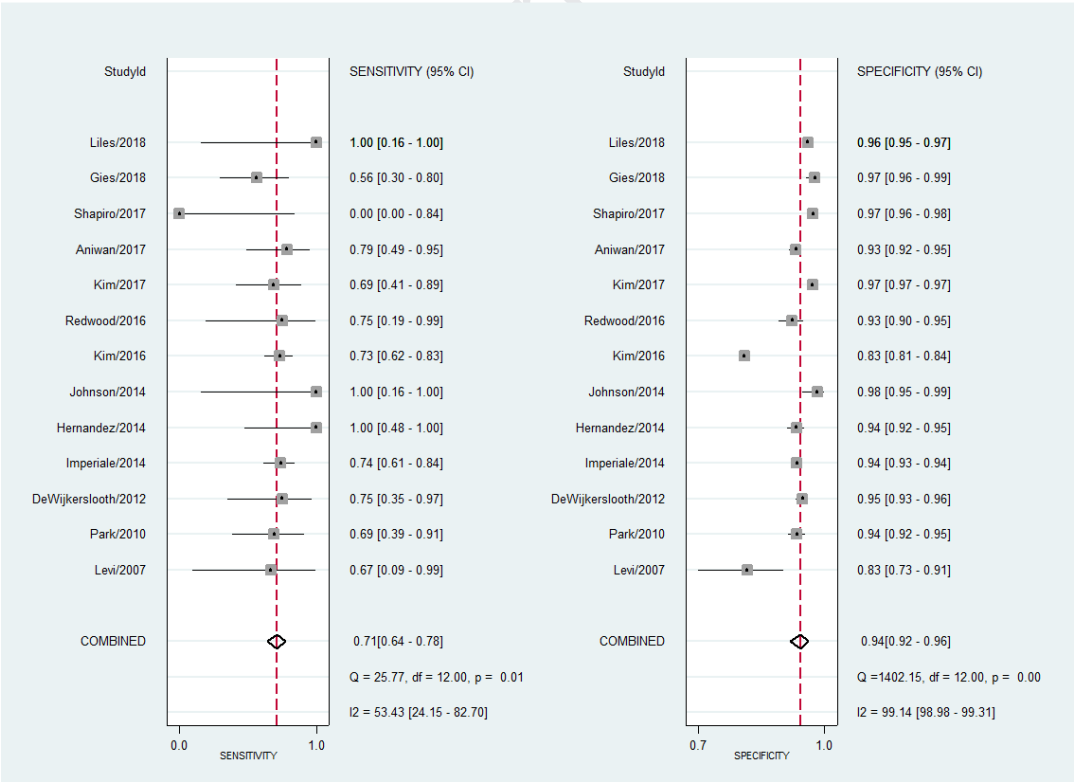
Supplemental materials for "Accuracy of the Quantitative Fecal Immunochemical Test…"

Figures 10A-B: Colorectal cancer detection of the OC-Sensor test using all available positivity thresholds from only studies with colonoscopy follow-up

A. Positivity thresholds ≤10 µg/g

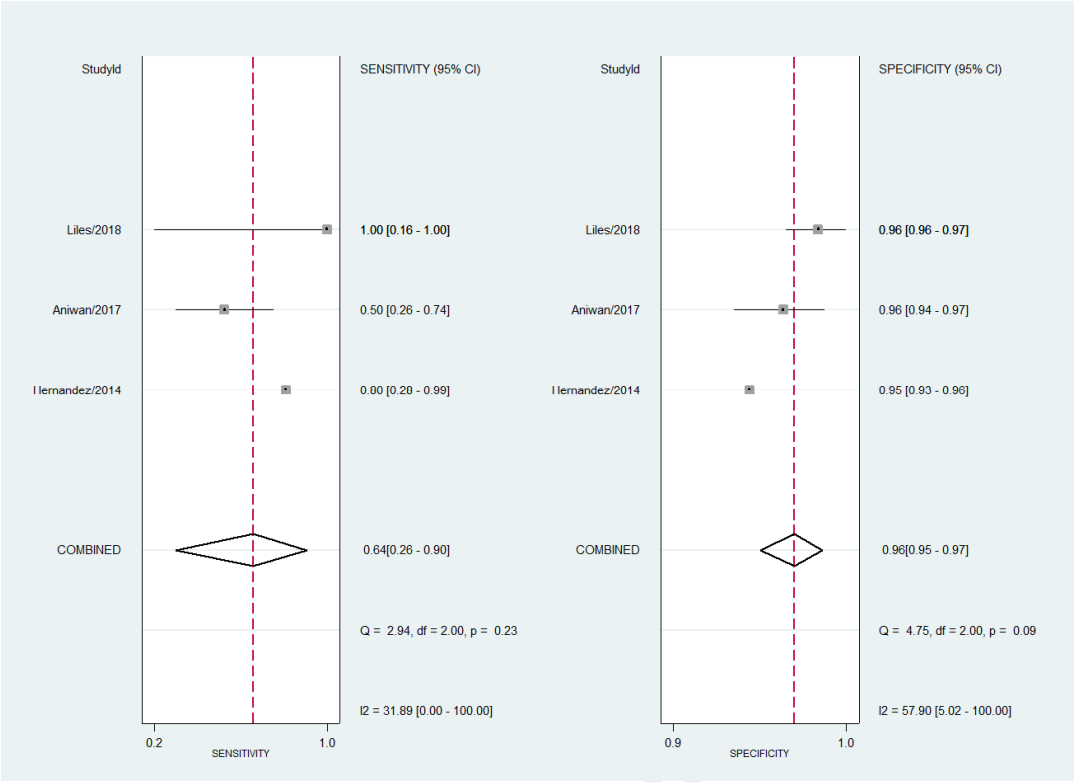


B. Positivity thresholds >10 and ≤20 µg/g



Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

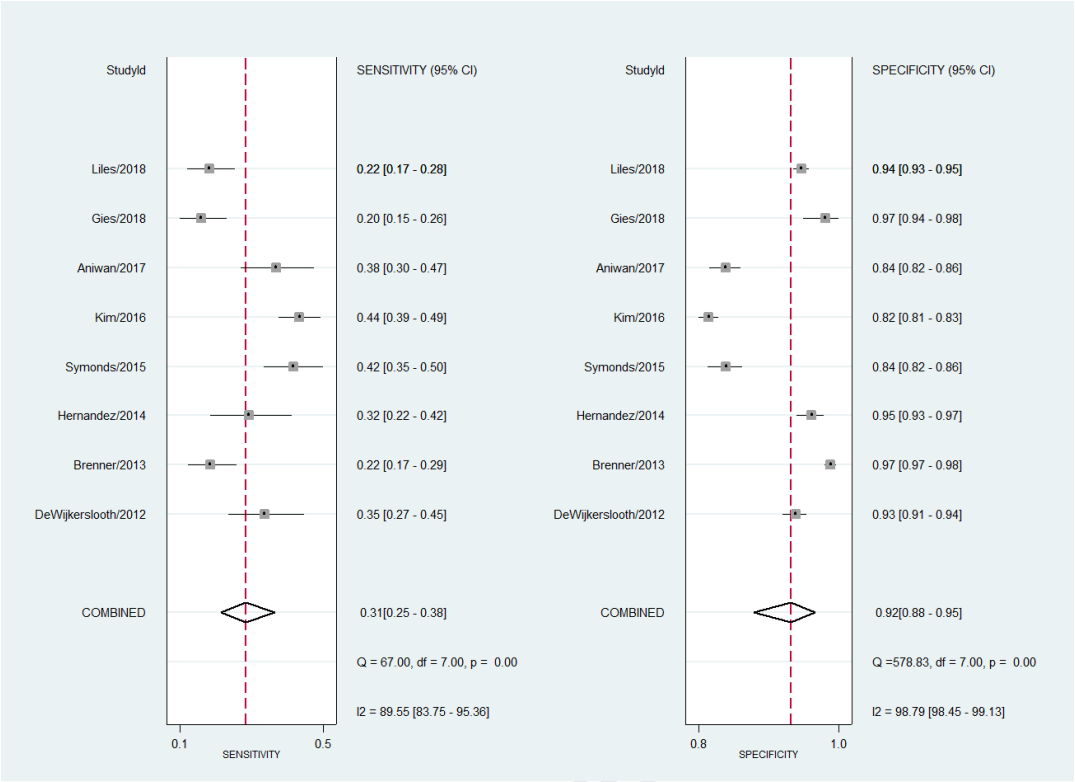
C. Positivity thresholds >20 µg/g



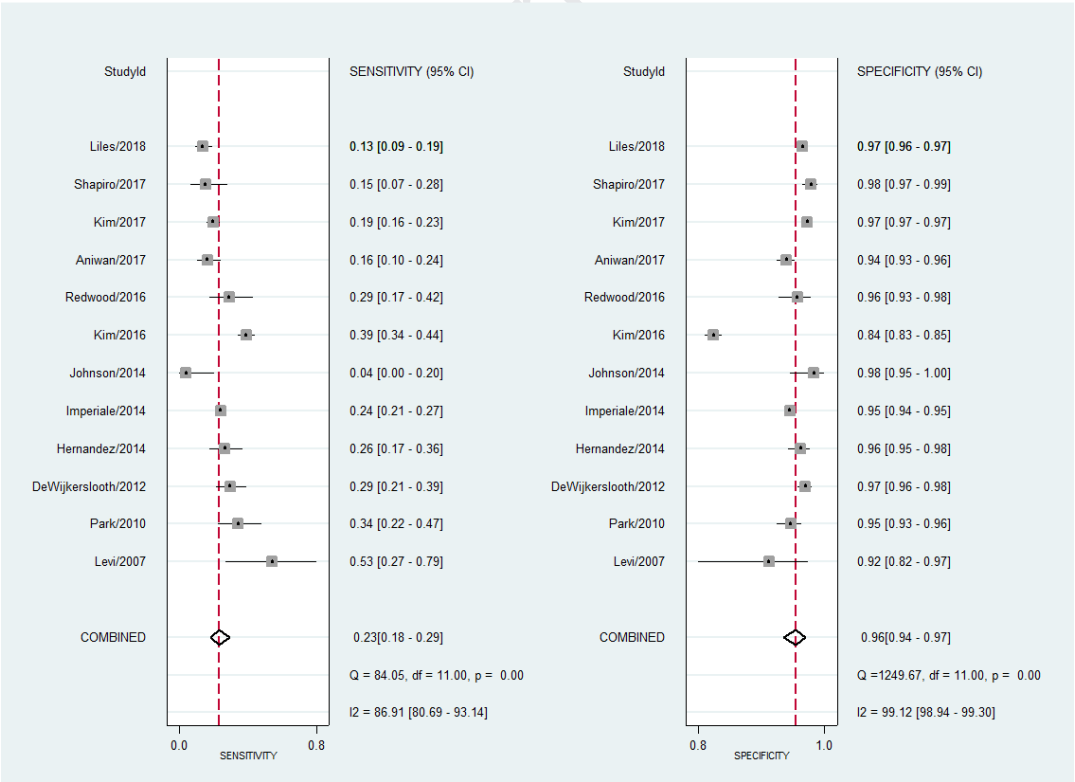
Supplemental materials for "Accuracy of the Quantitative Fecal Immunochemical Test…"

Figures 11A-B: Advanced adenoma detection of the OC-Sensor test using all available positivity thresholds from only studies with colonoscopy follow-up. Pooled analyses were not possible >20 µg/g because of inadequate number of studies.

A. Positivity thresholds ≤10 µg/g



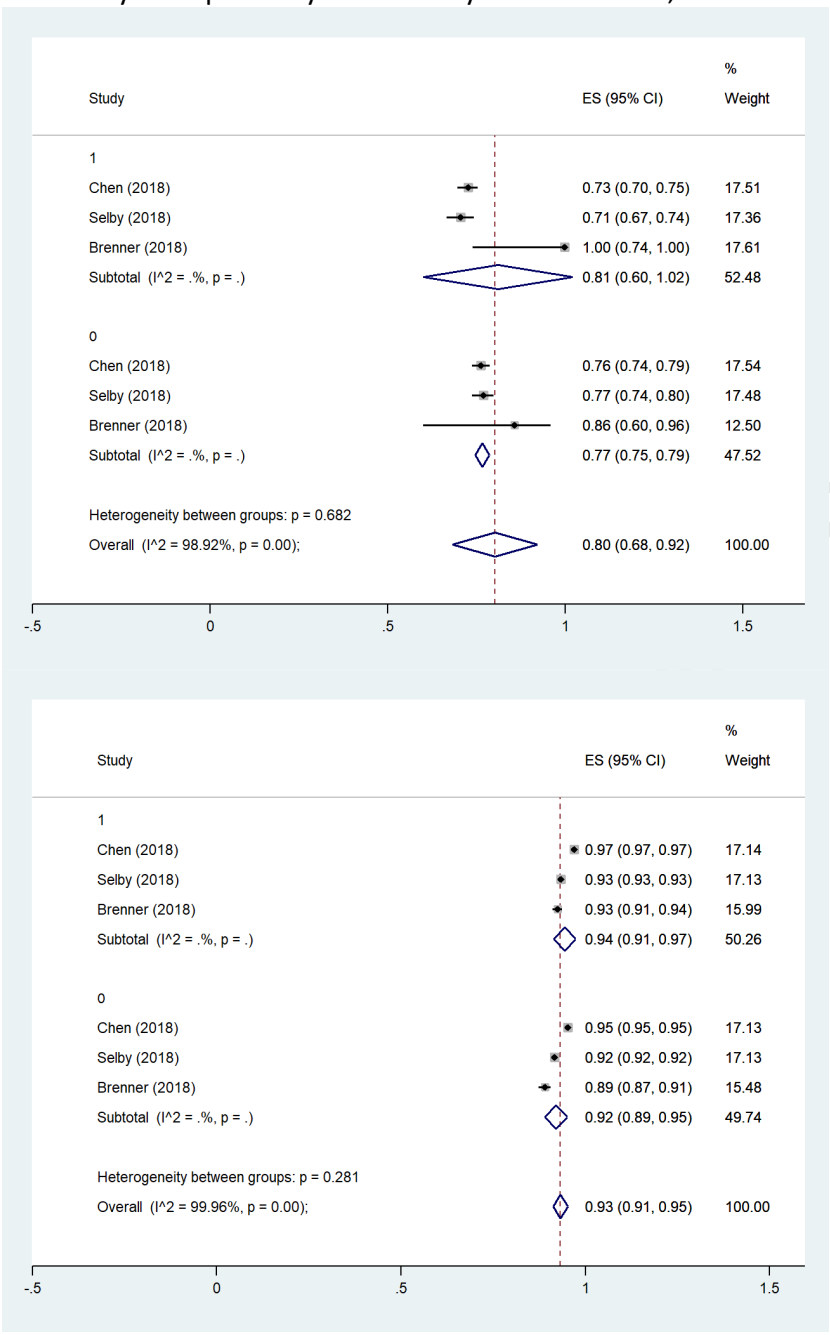
B. Positivity thresholds >10 and ≤20 µg/g



Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

Figures 12A-B: Colorectal cancer detection in studies that stratified by sex and age. Details of studies in Table 3.

A. Sensitivity and specificity stratified by sex. 1=women, 0=men



Supplemental materials for “Accuracy of the Quantitative Fecal Immunochemical Test…”

B. Sensitivity and specificity stratified by sex. 1=60-69 years, 0=50-59 years