OXFORD

BJS Open, 2025, zrae154
https://doi.org/10.1093/bjsopen/zrae154
Systematic Review

Diagnostic accuracy of the faecal immunochemical test and volatile organic compound analysis in detecting colorectal polyps: meta-analysis

Asma Afzal[1,2], Yekaterina S. Aranan[3], Tom Roberts[4], James Covington[5], Lorena Vidal[6], Sonia Ahmed[2], Talvinder Gill[1] and Nader Francis[3,7,*]

[1]Department of Colorectal Surgery, North Tees & Hartlepool NHS Foundation Trust, Stockton-on-Tees, UK
[2]School of Health & Life Sciences, Teesside University, Middlesbrough, UK
[3]Department of Surgery, Yeovil Hospital, Southwest Yeovil, UK
[4]Undergraduate Department, University of Bristol, Bristol, UK
[5]Department of School of Engineering, Warwick University, Warwick, UK
[6]Department of Analytical Chemistry, Nutrition and Food Science, University Institute of Materials and ISABIAL, University of Alicante, Alicante, Spain
[7]Department of Education and Research, Griffin Institute, London, UK

Correspondence to: Nader Francis, Department of Education and Research, Griffin Institute, Northwick Park and St Mark's Hospital, Y Block, Watford Road, London HA1 3UJ, UK (e-mail: n.francis@griffininstitute.org.uk)

Abstract

Background: For the early detection of colorectal cancer, it is important to identify the premalignant lesions to prevent cancer development. Non-invasive testing methods such as the faecal immunochemical test are well established for the screening and triage of patients with suspected colorectal cancer but are not routinely used for polyps. Additionally, the role of volatile organic compounds has been tested for cancer detection. The aim of this review was to determine the diagnostic accuracy of the faecal immunochemical test and volatile organic compounds in detecting colorectal polyps.

Methods: Original articles with diagnostic test accuracy measures for both the faecal immunochemical test and volatile organic compounds for advanced adenomas were included. Four databases including Medical Literature Analysis and Retrieval System Online (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, and Web of Science were searched. The quality assessment tool for diagnostic accuracy study was used to assess the risk of bias and applicability. Meta-analysis was performed using RStudio® and the combined faecal immunochemical test-volatile organic compounds sensitivity and specificity were computed.

Results: Twenty-two faecal immunochemical tests and 12 volatile organic compound-related articles were included in the systematic review whilst 18 faecal immunochemical tests and eight volatile organic compound-related studies qualified for the meta-analysis. The estimated pooled sensitivity and specificity of the faecal immunochemical test to diagnose advanced adenoma(s) were 36% (95% c.i. 30 to 41) and 89% (95% c.i. 86 to 91) respectively, with an area under the curve of 0.65, whilst volatile organic compounds pooled sensitivity and specificity was 83% (95% c.i. 70 to 91) and 76% (95% c.i. 60 to 87) respectively, with an area under the curve of 0.84. The combined faecal immunochemical test-volatile organic compounds increased the sensitivity to 89% with a specificity of 67%.

Conclusion: Faecal immunochemical testing has a higher specificity but poor sensitivity for detecting advanced adenomas, while volatile organic compound analysis is more sensitive. The combination of both tests enhances the detection rate of advanced adenomas.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths in Western countries, with 16 800 deaths every year in the UK[1–3]. It is expected that by 2030, the global burden will rise by 60% with over 2.2 million new patients and 1.1 million annual deaths, with the cost exceeding €238 777 per patient to treat advanced colorectal cancer[4,5]. According to the UK bowel cancer statistics, the estimated annual cost is more than 2.0 billion euros, and approximately 1:14 men and 1:18 women will develop colorectal cancer in their lifetime[1].

Colorectal cancer usually develops from polyp(s), which are one of the most common colorectal (CR) conditions and a leading factor for the development of colorectal cancer[6]. The rate of transformation of polyp to invasive cancer is thought to take 5–10 years but can be accelerated in cancer predisposition syndromes such as Lynch[7,8]. The core understanding of this process carries a significant clinical impact on patient care and early detection plays a crucial role[4,9,10].

Diagnosing CR neoplasms is difficult as colorectal symptoms are poor predictors of disease detection[11] and pose a greater challenge to deciding which patients to reassure or investigate[12]. The CR polyp prevalence in high-risk populations can reach up to 30%[13,14], however, an increasing prevalence is observed in younger populations (less than 50 years of age) with a prevalence of 33.1% for all types of polyps and 22.4% for precancerous polyps[15,16]. This has resulted in an increasing rate of colonoscopies and increased burden on endoscopy services.

Received: September 04, 2024. **Revised:** November 03, 2024. **Accepted:** November 10, 2024

Colonoscopy is the 'standard' investigation for suspected CR neoplasms, carrying 95% sensitivity and up to 92% specificity[17]. However, the procedure is invasive, requires bowel preparation and carries a small but significant risk of serious complications including bowel perforation[18], which limits its use as a primary triage tool.

Faecal immunochemical testing is widely used in the UK as a triage tool in both bowel cancer screening and fast-track pathways[19,20]. Despite the implementation of the fast-track '2-week wait' (2WW) pathway, studies have reported a 3–10% colorectal cancer diagnosis rate[21–23].

The National Institute of Clinical Excellence (NICE) recently updated guidelines (DG56) for faecal immunochemical testing of all patients regardless of high or low pretest probability for colorectal cancer[24,25]. However, the faecal immunochemical test (FIT) has highly variable sensitivity (5–67%) for colorectal cancer[26,27] and for advanced adenomas (AAs), ranging from 34% to 40%[28], with no significant enhanced effect on sensitivity by changing the threshold values[28]. It has a low patient adherence rate (47%), mainly due to stool-based sampling[29].

This represents an unmet need to identify a better triage tool for premalignant lesions with better acceptability for patients. Recently, interest in using volatile organic compound (VOC) analysis for the non-invasive detection of cancer from human waste has increased and its feasibility to detect colorectal cancer has been evaluated within the National Health Service (NHS) fast-track colorectal cancer pathways[30]. The ability to perform VOC analysis in urine distinguishes it from FIT and other non-invasive tests (faecal DNA/RNA), making it favourable in terms of feasibility and patient compliance. Global studies support VOC analysis as a potential future triage tool for cancer[31–36], however, its role in detecting premalignant lesions is still an area for research.

Although there have been several systematic reviews and meta-analyses on the role of FIT in detecting colorectal cancer[37–42], there is little synthesis on the role of FIT or VOC in detecting polyps.

The rationale for conducting this review was to synthesize and assess the quality of available diagnostic studies in evaluating the role of FIT and VOC alone or in combination for the early detection of colorectal polyps. The main objective was to evaluate the role of combined FIT and VOC in enhancing the detection of colorectal adenomas in different population groups to bridge the gap in the literature and provide guidance for future studies.

Methods

This systematic review was conducted according to recommendations from the Preferred Reporting Items for Systematic Review and Meta-analysis of Diagnostic Test Accuracy studies (PRISMA-DTA) 2018 statement[43] (*Fig. S1*).

The patient/target condition, index test, and outcome (PIO) framework was used to search the databases. The search terms 'colorectal polyp(s)', 'advanced adenoma', 'colorectal adenomas', 'faecal immunochemical test', 'volatile organic compound analysis', 'biomarkers', 'diagnostic accuracy' were used with synonyms for each word for effective database search (*Table S1*). A literature search of articles from Medical Literature Analysis and Retrieval System Online (MEDLINE)/CINHAL (Cumulative Index to Nursing and Allied Health Literature) through Elton B. Stephens Company (EBSCO) host, Embase (using Ovid) and Web of Science was performed (*Fig. S2*). The last date of the database search was 15 October 2024, with no restriction to the year of publication or language. Google Scholar and previous reviews[28,44] were also searched for grey literature.

One article included in this review was in the Chinese language[45], which was translated by Google Translator to extract the required data and for the quality assessment of the article. Where information was missing, or unpublished data was required, principal investigators (PIs) for each article were contacted via e-mail.

Study selection and quality assessment

Articles from all databases were added to EndNote® 20 and a two-phase screening process was completed according to PRISMA-DTA guidelines. During the first phase, data was screened based on the title and abstract followed by a second phase full-text article review of eligible studies. Apart from including primary studies on colorectal polyps, the articles primarily reporting colorectal cancer outcomes (for FIT or VOC analysis) were also reviewed based on inclusion criteria to extract polyp-related data. Only studies reporting both sensitivity and specificity for either test were included in the final analysis. Two independent reviewers completed the screening process and any discrepancy was resolved with the corresponding author for final inclusion in the systematic review and meta-analysis.

Quality assessment of diagnostic accuracy study-2 tool (QUADAS-2)[46] was used for risk of bias (RoB) and applicability assessment by two independent reviewers and any disagreement was resolved upon discussion with a third reviewer. The outcome for both RoB and applicability was expressed as 'high', 'low' or 'unclear'.

Data extraction

A structured data extraction form (*Table S2*) was used for data collection according to inclusion and exclusion criteria (*Table S3*). Prospective (cross-section/observational/case-control) studies including patients who underwent the FIT or testing for volatile compounds and had colorectal polyps confirmed through reference tests, that is colonoscopy/CT colonography or flexible sigmoidoscopy, were included. All retrospective studies including patients with colorectal cancer, or lack of reporting of diagnostic accuracy measures for AAs, were excluded.

Data synthesis and statistical analysis

Only studies with data for AAs were compiled for this systematic review and further meta-analysis. Any adenoma ≥1 cm in size (or), presence of villous features (or) high-grade dysplasia was classified as AA.

Studies reporting both sensitivity (Se) and specificity (Sp) with confidence interval (c.i.) related to AAs were included in the review and any additional information on accuracy or prevalence (P) was also added. True positives, true negatives and false positives/false negatives were calculated from Se and Sp data. Data was reported as per patient, that is, the number of patients diagnosed with at least one AA (one patient can have multiple adenomas and hence categorized based on the most advanced lesions present).

Only studies reporting both sensitivity and specificity data were included for further meta-analysis (MA). For FIT studies, the threshold was limited to 10 μg/g Hg, which is currently used for patients suspected of high-risk lesions in the NHS 2WW pathway. Because FIT sensitivity is low regardless of the threshold (7–20 μg/g Hg) and the chance of missing patients with high-risk polyps remains approximately three-quarters at the threshold of 120 μg/g Hg, which is currently used in the National Bowel Screening Programme[28,47], the data for both symptomatic and asymptomatic patients was collected at the threshold of 10 μg/g Hg.

Gas chromatography and mass spectrometry (GC-MS) is the 'standard' for VOC analysis; only studies with GC-MS were further included for MA pooling data from all sample types. Additional subgroup analysis of VOC studies was performed based on the sample type, that is breath, stool and urine.

The RStudio® software (v. 4.3.2) for bivariate analysis using the random-effects model (due to large interstudy variability which cannot be described by chance only as in the fixed-effect model) was used for meta-analysis to calculate pooled sensitivity and specificity for both FIT and VOC testing and these are presented as forest plots. The area under the curve (AUC) is represented by the summary receiver operating characteristic (SROC) curve. According to current PRISMA-DTA guidelines for systematic review and meta-analysis, the statistical analysis to estimate and report heterogeneity and publication bias is not very useful[43] and is rather misleading in the case of publication bias[48]. Whilst performing MA heterogeneity is computed automatically and is mentioned in this review for descriptive purposes only and the quality of data is mainly assessed by QUADAS-2.

Combined FIT-VOC diagnostic accuracy measures were calculated in both a parallel (the result of both VOC and FIT interpreted simultaneously) and serial way (if FIT is used first to guide the need for the second test, that is VOC) and interpreted using the 'OR' rule[49]. The 'OR' rule states that if both tests (FIT and VOC) are negative then the result is negative whilst if either test is positive then it is a positive diagnosis. Pre- and posttest probabilities were calculated using online MedCalc software (v. 22.023) and Fagan's nomogram.

Results

Screening and selection of studies

A total of 1093 articles were identified from all databases, of which 22 FIT-[45,47,50–69] and 12 VOC-related articles[27,30,52,70–78] were included in the final analysis for the systematic review and 18 FIT[45,50–52,54,55,57,58,60–69] and 8 VOC[27,30,52,70–73,76] studies for the meta-analysis. The PRISMA-DTA flowsheet[43] (*Fig. 1*) shows the outcome of the screening process according to the eligibility criteria. The total number of patients with AAs was 2963 in the FIT group and 918 in the VOC group, with a mean age of 55.7[56–77] and 64.7[62–70] years respectively. Consistency in reporting features of AA, that is a size of ≥1 cm, villous histology or high-grade dysplasia, was found across all studies. Unpublished data[30] and missing information[27] for two articles were received via e-mail from PIs of the studies.

Study characteristics

FIT articles summary characteristics

All data for FIT articles were collected at a threshold positivity of 10 μg/g Hg, with 18 studies using quantitative OC-Sensor[47,50,53,56,58,59,61,63–67], OC-Micro[55,68], HM-JACKarc Analyser[52,54] and others[45,51], whilst four studies used qualitative methods, that is OC-Light[57,62,69] and Hemosure[60] for FIT analysis. All studies were prospective except one, which was a randomized clinical trial[55], and eight studies were multicentre[47,50,52,59,61,65,66,68].

Most of the target population was mixed[45,53,55,59,61,63–65,68] followed by screening[47,56,60,62,67], symptomatic[50,51,54,58], surveillance[52,66] and asymptomatic[57]. Patients were mainly recruited from either primary[58,63] or secondary care[45,52,56,59,61,62,64,67,68] or both[50,51,65,66] and six studies[47,50,52,54,58,63] represented the UK population. Only seven studies[50,52,55,58,60,62,63] followed Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines. The funding source was declared by all except three studies[55,57,67] and all studies had ethical approval (*Table 1* and *Table S4*).

VOC articles summary characteristics

Only two studies followed STARD guidelines for reporting data[30,52]. Eight studies were multicentre[30,52,70–74,77] and all studies were prospective[30,52,71–73,75,77,78] except four studies which were mainly cross-sectional[27,74] and case-control designs[70,76]. The target population was mainly mixed[70,72,76,77] or screening[27,71,73,78] followed by symptomatic[30,74,75] population. Patients were referred or recruited from both primary and secondary care and five studies[30,52,72,73,75] represented the UK population.

Urine was the most common type of sample used[30,52,73,75,78] for VOC analysis followed by breath[71,72,74,76] and stool[27,70,77]. Slight variability in methodology and sample collection was observed and only two studies[27,52] mentioned the cut-off threshold of positivity, that is 8.4×10^8 and 0.88 (no units) respectively using the GC-MS technique for VOC analysis in AAs (*Table 2*). After initial analysis, quantification by GC-MS was done by eight studies[27,30,52,70–73,76] which were included for meta-analysis.

Six articles[27,30,52,71,76,78] mentioned the type of VOCs found in adenomas. Alcohol derivatives were most commonly present as VOC markers in adenomas, acetone being most common followed by ethanol (*Table S5* and *Table S6*).

Quality assessment

QUADAS-2 assessment of FIT-related articles

Twenty-two studies were assessed for quality; overall, studies were either unclear or at low RoB. Six studies[54,57–59,61,67] were at high RoB mainly due to concerns with patient selection, dropouts from the study or timing of index test, sample collection method and unblinded interpretation of index test, and two studies[54,61] had applicability concerns.

The unclear risk was mainly related to lack of clarity in the description of blinding of the index[47,52,54,55,57,59,63,66,69] and reference standard test[47,50,52–55,57,59,61,63,68,69], the quality of the colonoscopy, variability in describing the target condition, method of sample collection and consecutive sampling in selecting patients[45,47,50,52–54,56–59,62,64,69] (*Table S7*, *Fig. S3*).

QUADAS-2 assessment of VOC-related articles

Twelve studies were assessed for quality; overall, more studies had an unclear RoB than applicability concerns (*Table S8*, *Fig. S4*).

Those with unclear RoB were mainly due to a lack of clarity in consecutive sampling, description of the target condition[27], inappropriate exclusions, blinding of the index[27,52,70–72,76,78], or reference standard test interpretation[27,52,70,72,76,78]. All studies mentioned the timing for the sample collection mainly 2–4 weeks before colonoscopy except two studies[30,71]. Moreover, there was variation in sample collection and storage conditions, and it remained unclear if this could impact the quality of data reported for VOCs.

Results of meta-analysis

Eighteen articles qualified for FIT analysis. The estimated pooled sensitivity was 36% (95% c.i. 30 to 41) whilst specificity was 89% (95% c.i. 86 to 91) from FIT studies with an AUC of 0.65 (*Fig. 2a* and *2b*). Substantial heterogeneity and variance were found among studies both in sensitivity (Higgins $I^2 = 72\%$, $\tau 2 = 0.14$) and specificity (Higgins $I^2 = 93\%$, $\tau 2 = 0.31$) data. This variability could be due to the population, qualitative or quantitative, method of FIT analysis or blinding (see details in quality assessment of studies).

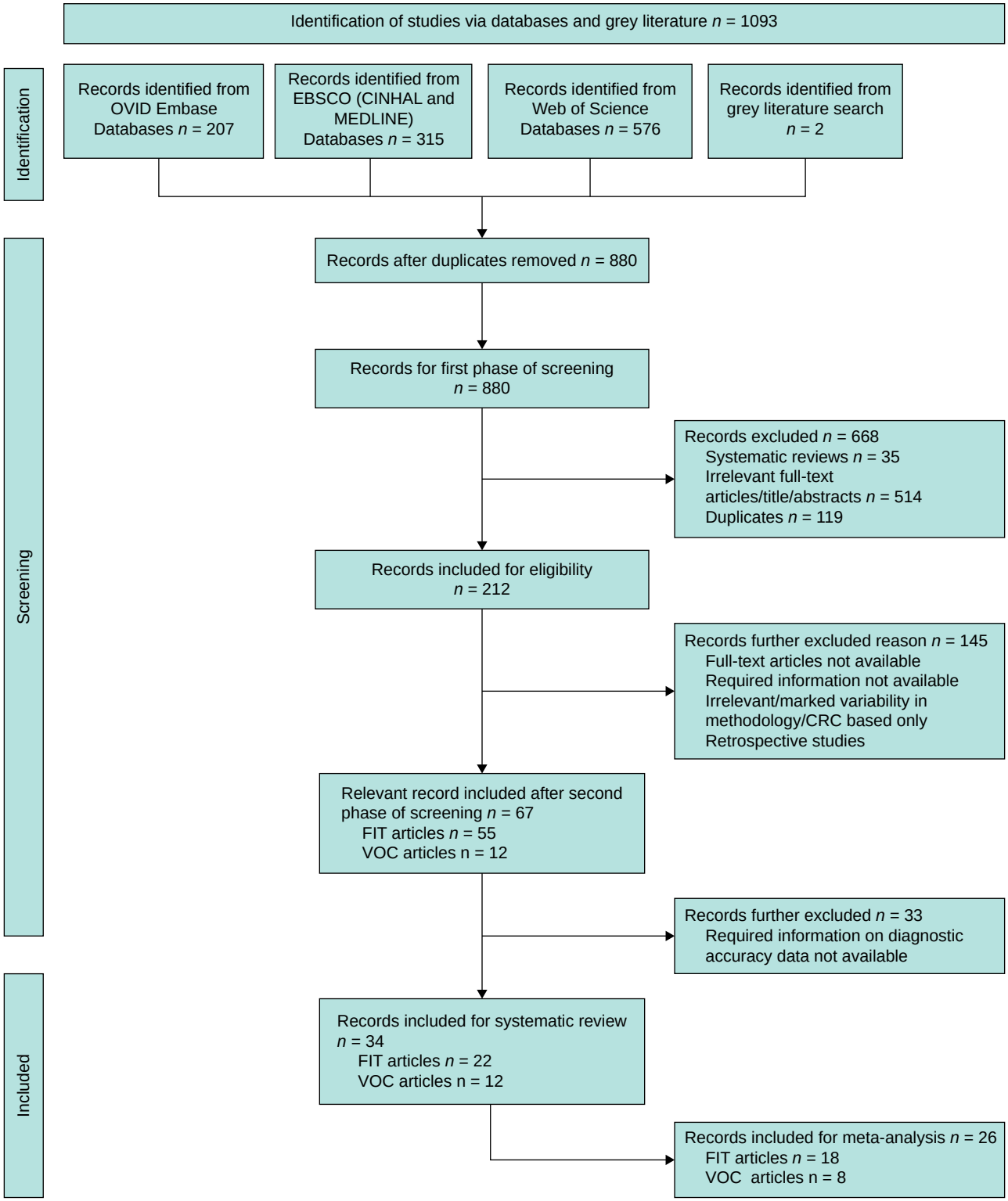

Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy (PRISMA-DTA) flow chart of screening process

FIT, faecal immunochemical test; VOC, volatile organic compound; OVID Embase, Ovid Excerpta Medica Database; EBSCO, Elton B. Stephens Company; CINHAL, Cumulative Index to Nursing and Allied Health Literature; CRC, colorectal cancer.

Eight studies qualified for VOC meta-analysis, and the pooled sensitivity was significantly higher, that is 83% (95% c.i. 70 to 91) with a specificity of 76% (95% c.i. 60 to 87) and AUC of 0.84 (*Fig. 3a* and *3b*). Substantial heterogeneity and variance in studies both in sensitivity (Higgins $I^2 = 85\%$, $\tau 2 = 0.86$) and specificity (Higgins $I^2 = 91\%$, $\tau 2 = 0.53$) were observed.

Sample-based subgroup analysis of VOC testing

Stool

Two studies including 76 patients with AA in stool-based sample analysis of VOC showed a pooled Se of 92% (95% c.i. 68 to 98) and Sp of 83% (95% c.i. 40 to 97) (*Fig. 4a*).

Table 1 Summary of analytical technique and diagnostic accuracy of faecal immunochemical test (FIT) studies (all data for FIT articles were collected at a threshold positivity of 10 μg/g Hg)

Author, year	Analytical technique	Total no. of patients	No. of patients with AA	Definition of adenoma(s)	Sensitivity, % (95% c.i.)	Specificity, % (95% c.i.)	AUC (95% c.i.)
Bath *et al.*, 2023[50]	OC-Sensor	553	47	UK and ESGE (unspecified) LRA = 1–2 adenomas each small size <1 cm IRA = 3–4 small or 1 adenoma ≥1 cm HRA = 5 small or ≥3 adenoma at least one ≥1 cm	42 (35,48)	81 (79,82)	0.63
Hijos-Mallada *et al.*, 2023[51]	FOB Turbilatex®	323	53	ESGE guidelines HRA = 5 small or ≥1 cm or HGD, SL ≥ 1 cm or with dysplasia	47 (33,60)	81 (76,85)	0.71 (0.63,0.78)
Chandrapalan *et al.*, 2022[52]	HM-JACKarc Analyser	141	68	BSG guidelines HRA = 5 small or ≥2 adenoma at least one ≥1 cm size	54 (43,65)	79 (73,84)	0.67
Zhou *et al.*, 2022[45]	Hs-qFIT	910	61	AA = ≥1 cm, VA, TVA (>25% VA) or HGD	23 (13,35)	94 (92,95)	Not reported
Li *et al.*, 2021[47]	OC-Sensor	3423	261	BSG guidelines	77 (68,85)	Not reported	Not reported
Sekiguchi *et al.*, 2021[53]	OC-Sensor	476	102	AA = ≥1 cm, HGD or prominent villous component	18 (11,27)	Not reported	Not reported
Farrugia *et al.*, 2020[54]	HM-JACKarc Analyser	473	18	HRA = ≥1 cm (6 patients had TVA)	30 (21,41)	79 (75,83)	Not reported
Mattar *et al.*, 2020[55]	OC-Auto Micro 80	141	37	AA = ≥1 cm, VA, TVA (>25% VA) or HGD Early adenomas = <1 cm and LGD	24 (10,45)	86 (77,92)	Not reported
Chang *et al.*, 2017[56]	OC-Sensor	4516	339	WHO criteria AA = ≥1 cm or HGD or VA	32 (27,37)	Not reported	Not reported
Teixeira, 2017[57]	OC-Light	171	123	Based on histopathology = HGD as HRA	26 (19,35)	83 (77,88)	Not reported
Mowat *et al.*, 2016[58]	OC-Sensor	241	40	AA = >3 adenomas or any adenoma ≥1 cm	50 (34,65)	78 (72,83)	Not reported
Symonds *et al.*, 2016[59]	OC-Sensor	1381	170	AA = ≥1 cm or >20% VA, or HGD, > 2 TA or stage 0 cancer	43 (36,51)	Not reported	Not reported
Wong *et al.*, 2015[60]	Hemosure	3643	269	AA = ≥1 cm, VA or TVA or HGD	33 (27,39)	91 (90,92)	Not reported
van Turenhout *et al.*, 2014[61]	OC-Sensor	2049	304	AA = ≥1 cm, VA or TVA or HGD	34 (30,41)	92 (91,93)	0.66
Chiu *et al.*, 2013[62]	OC-Light	1330	632	WHO criteria AA =≥1 cm or HGD or VA	28 (25,31)	93 (93,93)	Not reported
McDonald *et al.*, 2013[63]	OC-Sensor	194	23	BSG guidelines HRA = any adenoma ≥1 cm or ≥3 adenoma	47 (27,67)	96 (93,98)	Not reported
Ou *et al.*, 2013[64]	OC-Sensor	321	39	AA = ≥1 cm, VA or TVA or HGD	38 (23,55)	92 (89,94)	0.74
Terhaar sive Droste *et al.*, 2012[66]	OC-Sensor	935	101	AA = ≥1 cm, VA or TVA or HGD	28 (19,38)	91 (89,93)	Not reported
Terhaar sive Droste *et al.*, 2011[65]	OC-Sensor	236	97	AA = ≥1 cm, VA or TVA or HGD	41 (34,47)	90 (88,91)	Not reported
Khalid-de Bakker *et al.*, 2011[67]	OC-Sensor	243	38	AA = ≥1 cm, or any VA or HGD	15 (6,31)	96 (94,98)	Not reported
Rozen *et al.*, 2010[68]	OC-MICRO	1533	129	AA = ≥1 cm or >20% VA, or HGD	36 (28,44)	93 (92,94)	0.73 (0.68–0.78)
Gimeno-García *et al.*, 2009[69]	LA-FOBT (OC-Light)	67	12	AA = ≥1 cm, VA or HGD	83 (55,95)	91 (85,95)	Not reported

Values are *n* unless otherwise indicated. LRA, low-risk adenoma; IRA, intermediate-risk adenoma; HRA, high-risk adenoma; HGD, high-grade dysplasia; SL, serrated lesions; VA, villous adenoma/architecture; TVA, tubulo-villous adenoma; LGD, low-grade dysplasia; TA, tubular adenoma; AA, advanced adenoma; AUC, area under the curve; ESGE, European Society of Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology; WHO, World Health Organization.

Breath

Three studies including 419 patients, using breath analysis of VOC, showed a pooled Se of 75% (95% c.i. 61 to 84) and Sp of 89% (95% c.i. 24 to 95) (*Fig. 4b*).

Urine

Three studies including 370 patients with AA using urine samples had a pooled sensitivity of 82% (95% c.i. 53 to 95) and specificity of 69% (95% c.i. 60 to 76), closer to the pooled Se and Sp of VOC analysis than any other subgroup (*Fig. 4c*).

Combined FIT-VOC analysis

When FIT was combined with the VOC test, a higher sensitivity of up to 89% was obtained but the overall specificity decreased to 67% from individual pooled values of FIT and VOC testing both in parallel and serial testing under the 'OR' rule (*Table S9*).

Pre- and posttest probability of FIT and VOC testing

The pooled prevalence of AA using FIT was approximately 15%. Using this prevalence rate, the posttest probability of FIT detecting AA was 30% while it was 10% in the case of a negative

Table 2 Summary of sampling and diagnostic accuracies of volatile organic compound analysis studies

Author, year	VOC source	Analytical technique and threshold	Definition of adenoma(s)	No. of patients with AA (total no. of patients)	Sensitivity, % (95% c.i.)	Specificity, % (95% c.i.)	AUC (95% c.i.)
Alustiza *et al.*, 2023[27]	Stool	GC-MS Cut point: 8.4×10^8 (unit missing)	Not defined (results reported for >1 cm or VA taken as HRA)	12 (56)	83 (68,98)	63 (46,79)	0.70 (0.53,0.86)
Boulind *et al.*, 2022[30]	Urine	GC-IMS	Not defined Number of AA (HGD/ > 1 cm size) confirmed from unpublished data	31 (65) unpublished data	84 (71,96) GC-MS unpublished data	70 (62,77) unpublished data	0.82
Chandrapalan *et al.*, 2022[52]	Urine	GC-MS Threshold for positivity = 0.88 (unit missing)	BSG guidelines HRA = 5 small or ≥2 adenoma at least one ≥1 cm	68 (141)	VOC alone 94 (88, 98) *In parallel testing* VOC-FIT combined sensitivity = 97	VOC alone 69 (64,75) *In parallel testing* VOC-FIT combined specificity = 11	0.74
Cheng *et al.*, 2022[71]	Breath	GC-MS	AA = ≥1 cm, VA and/or HGD	138 (222)	79 (72,85)	70 (60,79)	0.72
Woodfield *et al.*, 2022[72]	Breath	GC-MS	BSG guidelines HRA = 5 small or ≥2 adenoma at least one ≥1 cm or HGD or VA or SL with dysplasia	271 (628)	66 (60,71)	58 (52,63)	0.67
Bosch *et al.*, 2020[70]	Stool	GC-MS	ESGE guidelines AA = ≥1 cm or villous histology or HGD	64 (291)	96 (91,99)	93 (89,96)	0.96 (0.93,0.99)
Mozdiak *et al.*, 2019[73]	Urine	FAIMS/GC-IMS	BSG guidelines HRA = 5 small or ≥2 adenoma at least one ≥1 cm or HGD or VA or SL with dysplasia	55 (79)	58 (44,71)	62 (41,81)	0.61 (0.47,0.75)
van Keulen *et al.*, 2020[74]	Breath	e-nose	AA = ≥1 cm, TVA (>25% villous) or HGD	112 (447)	73	79	0.69
Widlak *et al.*, 2018[75]	Urine	FAIMS	HRA = ≥3 adenoma, or ≥1 cm or HGD or VA or SL	27 (562)	93 (81,100.0)	16 (13,20)	0.56 (0.45,0.68)
Amal *et al.*, 2016[76]	Breath	GC-MS	AA = >1 cm, HGD or VA	10 (209)	94	94	Not available
Wang *et al.*, 2014[78]	Urine	Nuclear magnetic resonance spectroscopy	AA = ≥1 cm, villous histology or HGD	70 (876)	82	51	Not available
de Meij *et al.*, 2014[77]	Stool	Cyranose 320 e-nose	AA = ≥1 cm, TVA (>25% villous) or HGD	60 (157)	62	86	0.79

Values are *n* unless otherwise indicated. VA, villous architecture; HRA, high-risk adenoma; HGD, high-grade dysplasia; SL, serrated lesions; TVA, tubulo-villous adenoma; VOC, volatile organic compound; AUC, area under the curve; IMS, ion-mobility spectrometer; FIT, faecal immunochemical test; BSG, British Society of Gastroenterology; ESGE, European Society of Gastrointestinal Endoscopy; GC-MS, gas chromatography and mass spectrometry; FAIMS, field asymmetric ion mobility spectrometry; AA, advanced adenoma.

test (*Tables S10* and *S11*). Using the posttest probability of FIT as the pretest probability for VOC (if negative) showed a further reduction of the probability of having the disease to 3% (*Fig. S5a* and *S5b*). For descriptive purposes, further analysis of the AA pooled prevalence from VOC data was done which showed a higher disease prevalence compared with FIT, however, using this prevalence rate the chance of having AA after VOC test positivity increased to 60% and reduced to 10% in the case of a negative result (*Fig. S6*).

Discussion

In this systematic review and meta-analysis, the evidence on diagnostic accuracy was synthesized for both FIT and VOC alone and in combination to detect advanced colorectal adenomas. The pooled estimates showed overall low sensitivity (36%, 95% c.i. 30 to 41) and high specificity (89%, 95% c.i. 86 to 91) of FIT at the threshold of 10 μg/g Hg to detect AA(s); this finding is comparable to the most recent review in 2020[28] on FIT performance which showed a sensitivity of AA in the range of 25–40% at a threshold of 10 μg/g Hg. The pooled estimate of VOC showed significantly higher sensitivity (83%, 95% c.i. 70 to 91) with slightly lower specificity (76%, 95% c.i. 60 to 87); this was a new finding in our review with no previous review available for comparison.

This marked difference in sensitivities of the two tests (FIT and VOC) could be explained by the different nature of these tests targeting different parts of the disease process. The VOC analysis detects alteration of the 'volatilome' of the individual carrying the disease, which starts at an early stage of the

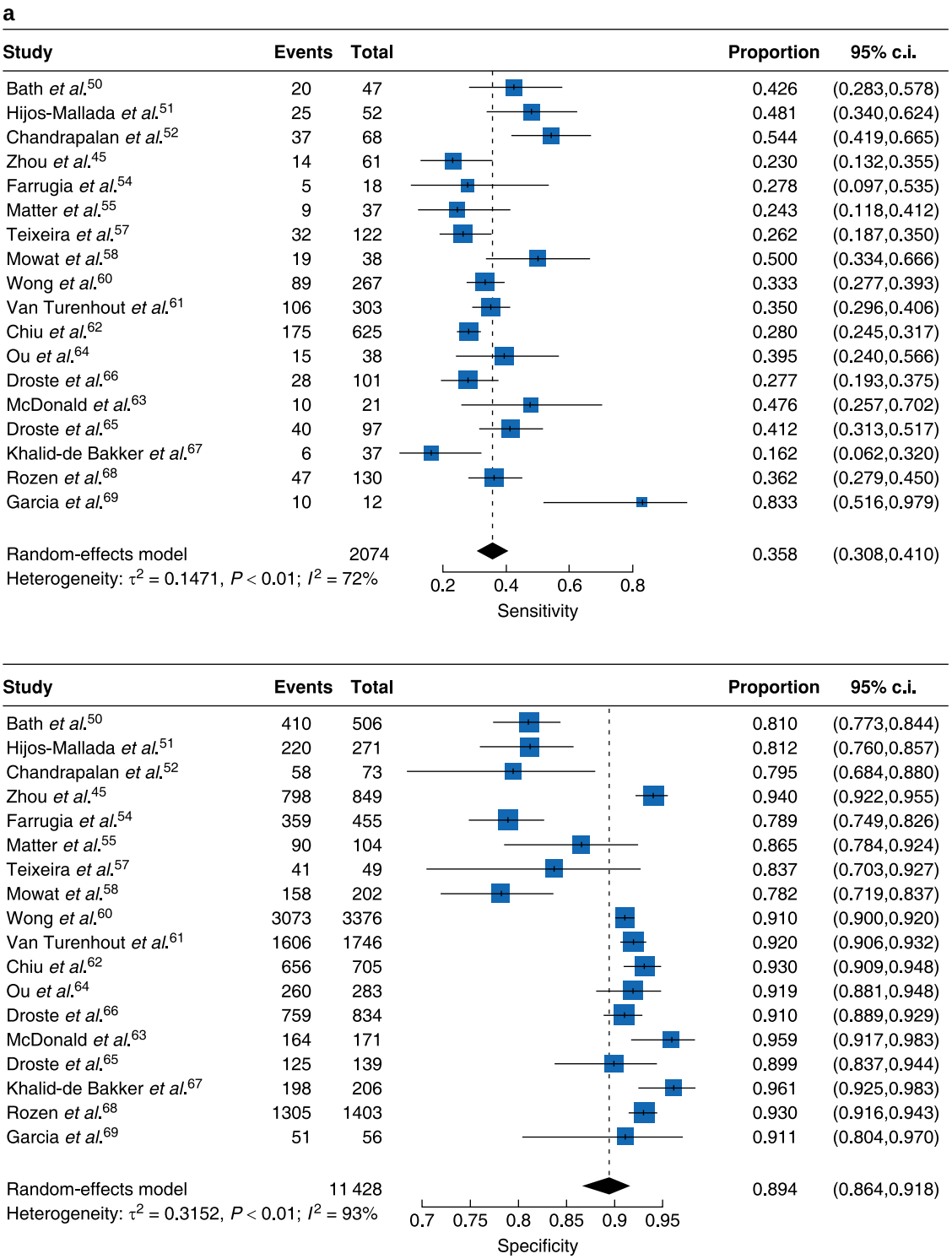

Fig. 2 Forest plot and summary receiver operative characteristic (SROC) of faecal immunochemical test (FIT)
a Forest plot using a random-effects model showing sensitivity and specificity of individual studies and corresponding 95% confidence interval (c.i.), with pooled sensitivity of 35% (95% c.i. 30 to 41) and specificity of 89% (95% c.i. 86 to 91) of FIT in detecting advanced colorectal adenomas. **b** SROC plot of sensitivity and specificity of FIT analysis. Each triangle represents an individual study. The small round spot on the SROC (solid purple line) represents summary sensitivity and specificity, with ellipse around showing the area of 95% confidence interval. The estimated area under the curve (AUC) is 0.65. (Continued on next page).

disease process and produces disease-specific patterns[7,27], whilst FIT is based on the detection of blood, which can be present in other conditions as well[7], and could be a late finding, missing 65–75% of the patients harbouring high-risk precancerous colorectal lesions[79].

Along with offering higher sensitivity, another strength of the VOC test is the ability to perform VOC analysis in stool, urine or breath samples. FIT is only carried out on stool samples, which over time has shown poor acceptability among the general population with a non-adherence rate of 76%, minimizing the

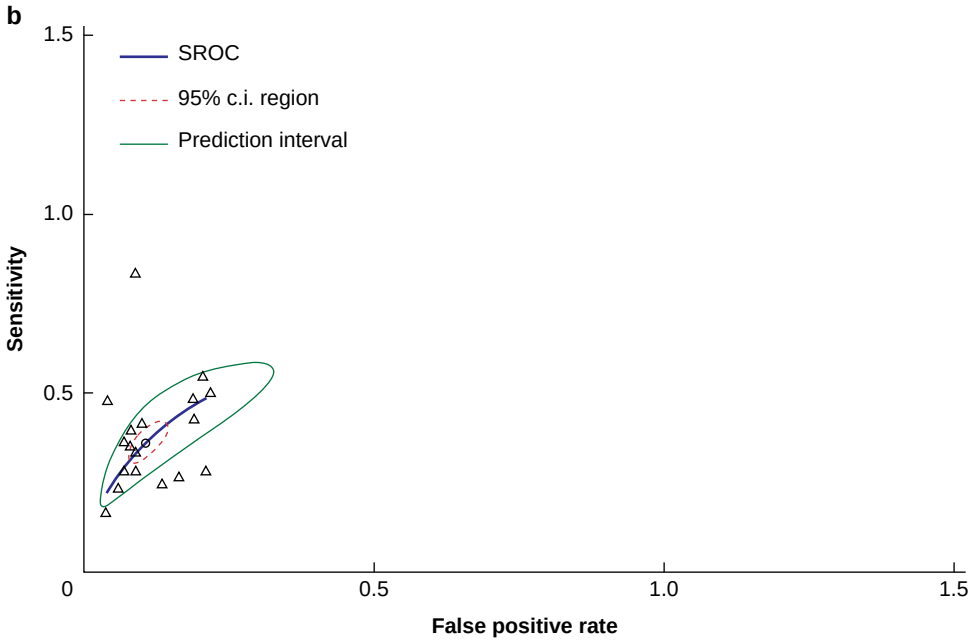

Fig. 2 Continued

benefits of the screening pathway[80]. Moreover, in a recent update, the uptake of FIT by the younger population was well below the target threshold[81].

On the other hand, breath sampling suffers from sample instability, offers lower concentrations in samples with a 10% failure rate[74], difficulty in quality control and standardization of sample collection along with the confounding effect of VOCs in the external environment[82]. In this review, sample-based subgroup analysis showed the diagnostic accuracy for urine sampling[30,52,73] for VOC analysis was closer to the overall pooled diagnostic accuracy measures than the stool sample group[27,70], while the latter group was limited by sample size and quality of the study. The sample size for the breath analysis group was the highest, but it showed less sensitivity than pooled estimates, which could be explained by loss of VOC concentration during the collection process; however, this cannot be said with certainty and is an area of further research. Recent studies conducted on urine samples have shown promising results and feasibility[30,83], advocating its use in the 2WW pathway. Based on literature evidence and review findings, we suggest using urine as a preferable sample.

It was also demonstrated that the combination of FIT-VOC enhanced the overall sensitivity of detecting AAs. FIT has been studied previously in combination with other non-invasive modalities to increase its sensitivity for both colorectal cancer and adenomas. In a large prospective Deep-C study[84] combined mitochondrial DNA-FIT (Cologuard) had a sensitivity of 47% only for precancerous lesions, and in another review with no improvement[85]. The findings suggest that the FIT-VOC combination yields maximal sensitivity (89%) compared with other non-invasive modalities, with the additional advantage of urine-based sampling with easier collection[86] and increased patient acceptability.

The significance of an index test depends on its discriminatory power to classify disease from non-diseased patients, which can be analysed by the AUC[87]. According to SROC bivariate analysis in this review, the VOC test offers diagnostic accuracy with an AUC of 0.84, which suggests the significant ability of the VOC test in distinguishing patients with AAs from non-diseased patients, whilst FIT has a poor AUC (0.65), indicating its unsatisfactory diagnostic performance in clinical practice.

The VOC test can reduce the probability of missing patients with AA to 3%. This was depicted in posttest probability nomograms in which the chance of having AA doubled after FIT or VOC test positivity. However, in the case of a negative FIT test the posttest probability of having disease remained at 10% (which is still significant with the prevalence of AA at 15%), while it was reduced to 3% in the case of a negative VOC test, and these values are comparable to findings in a comparative analysis of FIT and VOC testing[7]. This could have implications in reducing false negative rates and patient safety concerns and increasing reassurance in average-risk adults.

Although diagnostic accuracy for polyps at various threshold levels was not explored in this review, previous studies suggest that a threshold of 120 μg/g Hg (used in the UK screening population) missed over half of the colorectal cancer and three-quarters of high-risk adenoma patients with a sensitivity of 25% reported at 120 μg/g Hg and for colorectal cancer 47.8%[47]. A few countries are now using the FIT threshold of 20 μg/g Hg in the screening population[88,89]; whether this can be applied to the UK remains an area of further research. Even though most of the population representation was mixed in this review, the pooled prevalence and FIT sensitivity were not different when compared with previous research articles[50,90] and review findings[28].

As colorectal cancer mainly develops from adenomas, it is important to detect precancerous lesions for cancer prevention and crucial that the test used for initial stratification will not miss a disease when it is present[91]. Demand for colonoscopies in the UK continues to increase, and each colonoscopy performed in the NHS outpatient department costs €665[92]. The adenoma miss rate among trained colonoscopists remains at 26–62%[93], which is the main cause of interval cancer[94]. However, it is not clear whether increasing the sensitivity of a test to detect

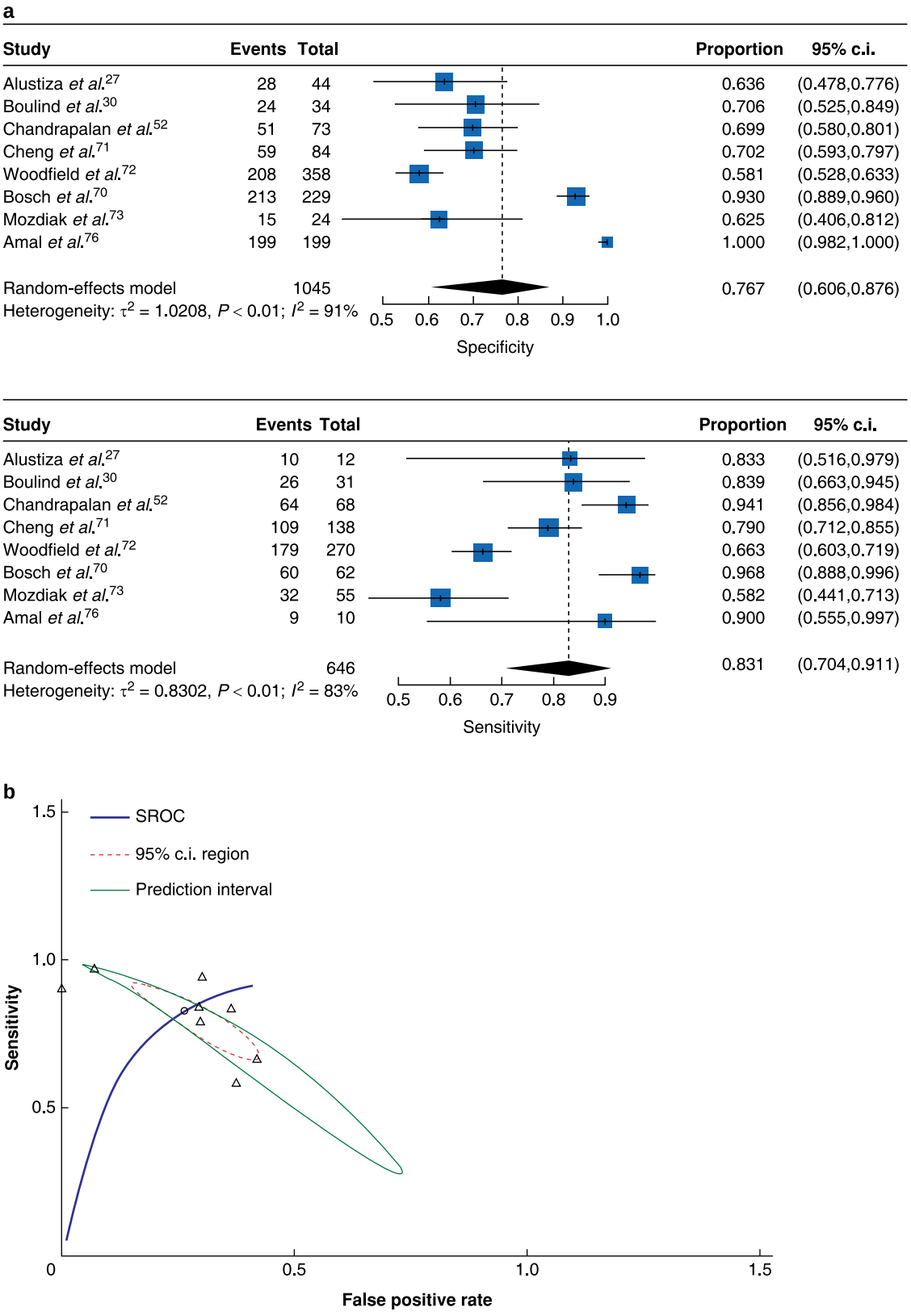

Fig. 3 Forest plot and summary receiver operative characteristic (SROC) of volatile organic compound (VOC) analysis. a Forest plot using a random-effects model showing sensitivity and specificity of individual studies and corresponding 95% confidence interval (c.i.), with a pooled sensitivity of 83% (95% c.i. 70 to 91) and specificity of 76% (95% c.i. 60 to 87) of volatile organic compounds in detecting advanced colorectal adenomas. **b** SROC plot of sensitivity and specificity of VOC analysis. Each triangle represents an individual study. The round spot on the SROC (solid purple line) represents summary sensitivity and specificity. The estimated area under the curve (AUC) is 0.84.

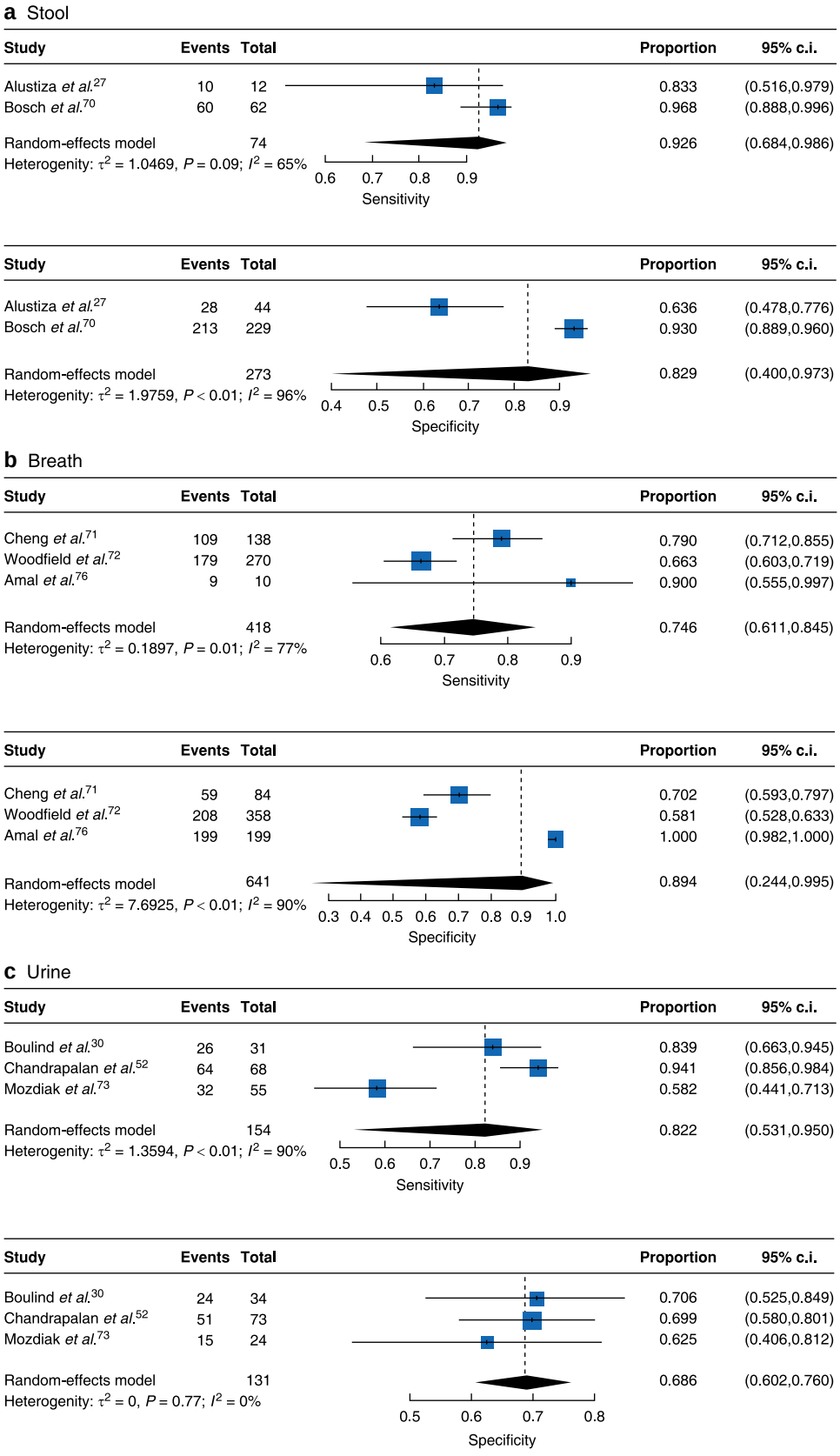

Fig. 4 Subgroup analysis of volatile organic compound (VOC) analysis. a Subgroup analysis of studies with stool sample used for VOC analysis. **b** Subgroup analysis of studies with breath sample used for VOC analysis. **c** Subgroup analysis of studies with urine sample used for VOC analysis.

adenomas would increase the adenoma detection rate, and this is an area for further research.

Using FIT alone for triage could miss more than half of the advanced polyps[50], therefore, a better triage tool is required with high sensitivity and more acceptability, and considering our review findings we recommend the VOC test alone or in combination with FIT in the fast-track pathway to aid early detection of high-risk polyps. Full healthcare economic research is required to establish the cost-effectiveness of the combination of VOC and FIT as a triage test but is expected to be less expensive than an upfront colonoscopy strategy. As VOC analysis can be done on urine samples this could increase patient acceptability.

In clinical practice, despite the huge amount of work on other non-invasive methods, FIT is still used as a standard triage tool in the NHS fast-track pathway. Although it is preliminary to add VOC in clinical pathways and further studies are required to validate the findings, however, based on the review findings we propose the following pathway (*Fig. 5*) to introduce VOC as a triage tool alone or in combination with FIT to increase the overall sensitivity of detecting AA(s) to prevent colorectal cancer. This may be more applicable to symptomatic/surveillance[52] or younger asymptomatic populations with a polyp prevalence of 15–30%[16] or where the screening threshold for FIT is low. It is too early to draw conclusions and further validation studies are required.

VOC testing is a non-invasive potential future triage tool, and its introduction in a fast-track pathway, alone or in combination with FIT can offer the following main benefits:

- Subjects with a negative FIT undergo further VOC testing which if positive mandates a referral for colonoscopy to help in the early detection of lesions.
- The combination of FIT-VOC in a fast-track pathway (especially FIT-negative symptomatic patients) will provide more reassurance, significantly reduce the false negative rate and increase patient safety.
- In the long term it will reduce the number of advanced lesions or colorectal cancer burden hence reducing morbidity rate and mortality rates.

GC-MS is recommended as the 'standard' and is advocated to be used for future studies in order to define thresholds for both colorectal cancer and adenomas. Urine testing for VOC analysis can be a preferable sample type to increase patient compliance in screening pathways. Due to technological considerations, sample analysis in centralized laboratory systems with networks/hubs will be required.

There were several limitations in this review. Data was limited to AAs as most of the studies were designed to primarily collect and report data on colorectal cancer and polyp data was secondarily reported with most studies reporting outcomes on AAs only. In addition, due to limited information, the ability to classify adenomas according to anatomical location (right- or left-sided) could not be reported.

Due to a lack of information, a detailed evaluation of threshold concentrations and chemical analysis for VOC for AA(s) could not be performed. The studies were mainly prospective with a lack of comparative or randomized clinical study designs of FIT and VOC tests. Another difficulty was presenting data in various population groups (that is, screening/symptomatic/surveillance) as most of the studies recruited a mixed population (with mostly symptomatic/surveillance patients) for both FIT and VOC data with a lack of reporting of diagnostic accuracies on individual groups for polyps.

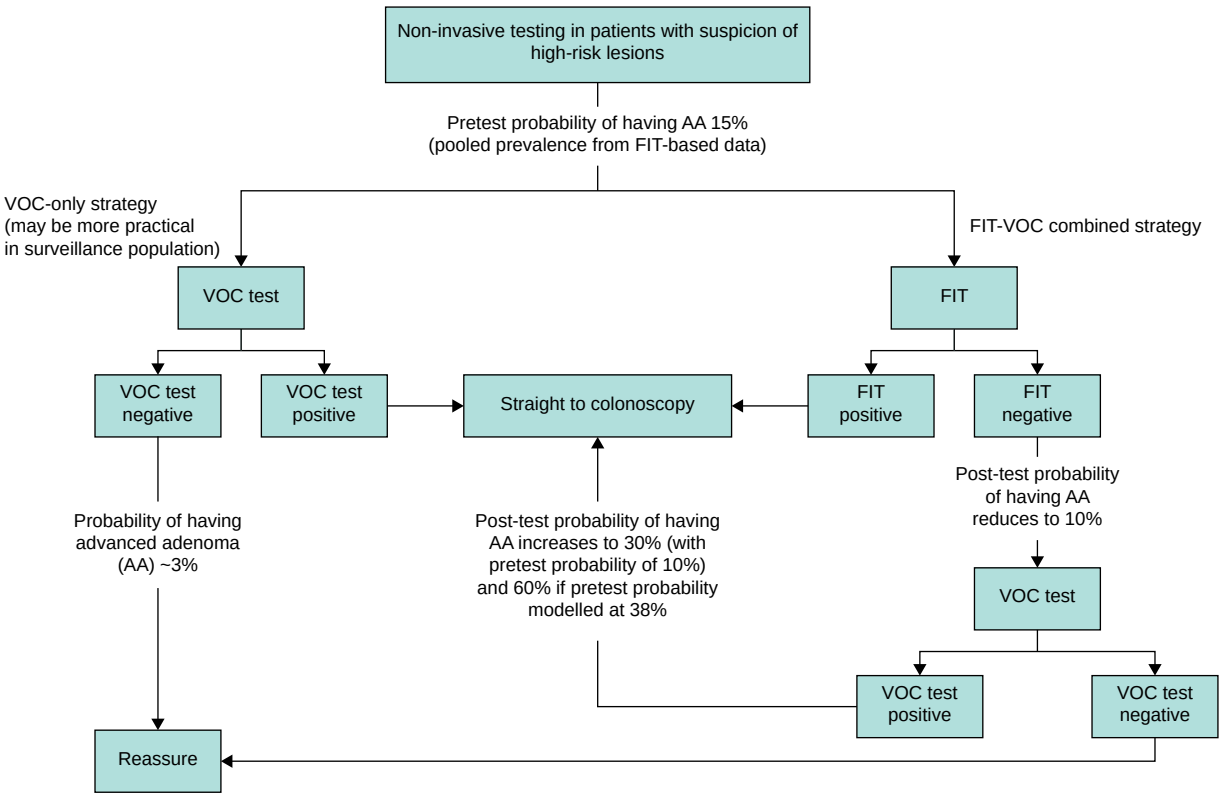

Fig. 5 Proposed algorithm for FIT and VOC testing as a triage tool for advanced colorectal adenomas

VOC, volatile organic compound; FIT, faecal immunochemical test; AA, advanced adenoma.

The data was of moderate quality, with most of the studies showing unclear RoB. The quality of statistical reporting in most of the articles was inadequate with a lack of confidence interval and contingency tables, due to which calculation of detailed values were computed from the best available information from studies included in this review. Therefore, slight variation in numbers is possible; however, effort has been made to ensure the accuracy of data and this has been re-checked to maintain the quality of the review.

Funding

The authors have no funding to declare.

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The authors confirm that the data supporting the findings of this review are available within the article and its supplementary material.

Author contributions

Asma Afzal (Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Visualization, Writing—original draft, Writing—review & editing), Yekaterina Skvarkovskaia Aranan (Data curation, Methodology, Validation), Tom Roberts (Data curation, Methodology, Validation), James Covington (Supervision, Writing—review & editing), Lorena Vidal (Writing—review & editing), Sonia Ahmed (Methodology, Supervision, Writing—review & editing), Talvinder Gill (Supervision, Writing—review & editing) and Nader K. Francis (Conceptualization, Methodology, Project administration, Supervision, Writing—review & editing)

References

1. Cancer Research UK. Bowel cancer incidence statistics. 2022. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-One. (Accessed 8 January 2024)
2. Medical Advisory Secretariat. Screening methods for early detection of colorectal cancers and polyps: summary of evidence-based analyses. *Ont Health Technol Assess Ser* 2009;**9**:1–65
3. Tarazi M, Guest K, Cook AJ, Balasubramaniam D, Bailey CMH. Two- and five-year survival for colorectal cancer after resection with curative intent: a retrospective cohort study. *Int J Surg* 2018;**55**:152–155
4. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol* 2019;**14**:89–103
5. Triantafillidis JK, Vagianos C, Malgarinos G. Colonoscopy in colorectal cancer screening: current aspects. *Indian J Surg Oncol* 2015;**6**:237–250
6. Soares F, Becker K, Anzanello MJ. A hierarchical classifier based on human blood plasma fluorescence for non-invasive colorectal cancer screening. *Artif Intell Med* 2017;**82**:1–10
7. Chandrapalan S, Arasaradnam RP. Urine as a biological modality for colorectal cancer detection. *Expert Rev Mol Diagn* 2020;**20**:489–496
8. Shussman N, Wexner SD. Colorectal polyps and polyposis syndromes. *Gastroenterol Rep (Oxf)* 2014;**2**:1–15
9. Øines M, Helsingen LM, Bretthauer M, Emilsson L. Epidemiology and risk factors of colorectal polyps. *Best Pract Res Clin Gastroenterol* 2017;**31**:419–424
10. Ahnen DJ. The American College of Gastroenterology Emily Couric lecture—the adenoma–carcinoma sequence revisited: has the era of genetic tailoring finally arrived? *Am J Gastroenterol* 2011;**106**:190–198
11. Ford AC, Veldhuyzen van Zanten SJO, Rodgers CC, Talley NJ, Vakil NB, Moayyedi P. Diagnostic utility of alarm features for colorectal cancer: systematic review and meta-analysis. *Gut* 2008;**57**:1545–1553
12. Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. *Br J Gen Pract* 2011;**61**:e231–e243
13. Click B, Pinsky PF, Hickey T, Doroudi M, Schoen RE. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. *JAMA* 2018;**319**:2021
14. Liljegren A. Prevalence and incidence of hyperplastic polyps and adenomas in familial colorectal cancer: correlation between the two types of colon polyps. *Gut* 2003;**52**:1140–1147
15. Liu L, Nagel R, Verma S, Pinidiyapathirage J. Colorectal polyps in young adults: a retrospective review of colonoscopy data from Toowoomba and the Darling Downs. *Intern Med J* 2024;**54**:1471–1477
16. Rutter MD, East J, Rees CJ, Cripps N, Docherty J, Dolwani S *et al.* British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* 2020;**69**:201–223
17. Calanzani N, Chang A, Van Melle M, Pannebakker MM, Funston G, Walter FM. Recognising colorectal cancer in primary care. *Adv Ther* 2021;**38**:2732–2746
18. Kim SY, Kim HS, Park HJ. Adverse events related to colonoscopy: global trends and future challenges. *World J Gastroenterol* 2019;**25**:190–204
19. Saw KS, Liu C, Xu W, Varghese C, Parry S, Bissett I. Faecal immunochemical test to triage patients with possible colorectal cancer symptoms: meta-analysis. *Br J Surg* 2022;**109**:182–190
20. Symonds EL, Winter JM. FIT for colonoscopy: benefits of the faecal immunochemical test for triaging symptomatic patients. *Lancet Reg Health Eur* 2022;**23**:100528
21. Patel RK, Sayers AE, Seedat S, Altayeb T, Hunter IA. The 2-week wait service. *Eur J Gastroenterol Hepatol* 2014;**26**:1408–1414
22. Royle TJ, Ferguson HJM, Mak TWC, Simpson JA, Thumbe V, Bhalerao S. Same-day assessment and management of urgent (2-week wait) colorectal referrals: an analysis of the outcome of 1606 patients attending an endoscopy unit-based colorectal clinic. *Colorectal Disease* 2014;**16**:O176–O181
23. Vaughan-Shaw PG, Cutting JE, Borley NR, Wheeler JMD. Repeat 2-week wait referrals for colorectal cancer. *Colorectal Disease* 2013;**15**:292–297
24. NICE. Quantitative faecal immunochemical testing to guide colorectal cancer pathway referral in primary care. 2024. https://www.nice.org.uk/guidance/dg56/chapter/2-The-diagnostic-tests. (Accessed 22 August 2024)

25. Cole E, Narayanan D, Tiam RN, Shepherd J, Hajjawi MOR. Faecal immunochemical test (FIT) sensitivity; a five-year audit. *Br J Biomed Sci* 2024;**81**:12862
26. Nakama H, Zhang B, Zhang X. Evaluation of the optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer. *Eur J Cancer* 2001;**37**:398–401
27. Alustiza M, Ripoll L, Canals A, Murcia O, Martínez-Roca A, García-Heredia A *et al.* A novel non-invasive colorectal cancer diagnostic method: volatile organic compounds as biomarkers. *Clin Chim Acta* 2023;**542**:117273
28. Imperiale TF, Gruber RN, Stump TE, Emmett TW, Monahan PO. Performance characteristics of fecal immunochemical tests for colorectal cancer and advanced adenomatous polyps. *Ann Intern Med* 2019;**170**:319
29. Fisher DA, Karlitz JJ, Jeyakumar S, Smith N, Limburg P, Lieberman D *et al.* Real-world cost-effectiveness of stool-based colorectal cancer screening in a Medicare population. *J Med Econ* 2021;**24**:654–664
30. Boulind CE, Gould O, de Lacy Costello B, Allison J, White P, Ewings P *et al.* Urinary volatile organic compound testing in fast-track patients with suspected colorectal cancer. *Cancers (Basel)* 2022;**14**:2127
31. Aggio RBM, de Lacy Costello B, White P, Khalid T, Ratcliffe NM, Persad R *et al.* The use of a gas chromatography-sensor system combined with advanced statistical methods, towards the diagnosis of urological malignancies. *J Breath Res* 2016;**10**:017106
32. Arasaradnam RP, Covington JA, Harmston C, Nwokolo CU. Review article: next generation diagnostic modalities in gastroenterology—gas phase volatile compound biomarker detection. *Aliment Pharmacol Ther* 2014;**39**:780–789
33. Cauchi M, Weber CM, Bolt BJ, Spratt PB, Bessant C, Turner DC *et al.* Evaluation of gas chromatography mass spectrometry and pattern recognition for the identification of bladder cancer from urine headspace. *Anal Methods* 2016;**8**:4037–4046
34. Khalid T, Aggio R, White P, De Lacy Costello B, Persad R, Al-Kateb H *et al.* Urinary volatile organic compounds for the detection of prostate cancer. *PLoS One* 2015;**10**:e0143283
35. Silva CL, Passos M, Câmara JS. Investigation of urinary volatile organic metabolites as potential cancer biomarkers by solid-phase microextraction in combination with gas chromatography-mass spectrometry. *Br J Cancer* 2011;**105**:1894–1904
36. Dima AC, Balaban DV, Dima A. Diagnostic application of volatile organic compounds as potential biomarkers for detecting digestive neoplasia: a systematic review. *Diagnostics* 2021;**11**:2317
37. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer. *Ann Intern Med* 2014;**160**:171–181
38. Stonestreet J, Chandrapalan S, Woolley D, Uthman U, Arasaradnam RP. Systematic review and meta-analysis: diagnostic accuracy of faecal immunochemical testing for haemoglobin (FIT) in detecting colorectal cancer for both symptomatic and screening population. *Acta Gastroenterol Belg* 2019;**82**:291–299
39. Zhu MM, Xu XT, Nie F, Tong JL, Xiao SD, Ran ZH. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: a meta-analysis. *J Dig Dis* 2010;**11**:148–160
40. Westwood M, Lang S, Armstrong N, van Turenhout S, Cubiella J, Stirk L *et al.* Faecal immunochemical tests (FIT) can help to rule out colorectal cancer in patients presenting in primary care with lower abdominal symptoms: a systematic review conducted to inform new NICE DG30 diagnostic guidance. *BMC Med* 2017;**15**:189
41. Niedermaier T, Balavarca Y, Brenner H. Stage-specific sensitivity of fecal immunochemical tests for detecting colorectal cancer: systematic review and meta-analysis. *Am J Gastroenterol* 2020;**115**:56–69
42. Lu M, Luo X, Li N, Chen H, Dai M. Diagnostic accuracy of fecal occult blood tests for detecting proximal versus distal colorectal neoplasia: a systematic review and meta-analysis. *Clin Epidemiol* 2019;**11**:943–954
43. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T *et al.* Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA* 2018;**319**:388–396
44. van Liere ELSA, van Dijk LJ, Bosch S, Vermeulen L, Heymans MW, Burchell GL *et al.* Urinary volatile organic compounds for colorectal cancer screening: a systematic review and meta-analysis. *Eur J Cancer* 2023;**186**:69–82
45. Zhou RC, Wang PZ, Ma MJ, Meng FY, Li YY, Zhang Y *et al.* Comparative study of hypersensitive quantitative fecal immunochemical test and qualitative fecal occult blood test for colorectal cancer and advanced adenoma. *Zhonghua Yi Xue Za Zhi* 2022;**102**:3667–3672
46. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–565
47. Li SJ, Sharples LD, Benton SC, Blyuss O, Mathews C, Sasieni P *et al.* Faecal immunochemical testing in bowel cancer screening: estimating outcomes for different diagnostic policies. *J Med Screen* 2021;**28**:277–285
48. Leeflang MMG. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008;**149**:889
49. Weinstein S, Obuchowski NA, Lieber ML. Clinical evaluation of diagnostic tests. *AJR Am J Roentgenol* 2005;**184**:14–23
50. Bath MF, Malhi A, Ayling RM, Seward E, Pritchard-Jones K, Laszlo HE *et al.* Faecal immunochemical testing for haemoglobin in detecting bowel polyps in symptomatic patients: multicentre prospective cohort study. *BJS Open* 2023;**7**:zrac161
51. Hijos-Mallada G, Saura N, Lué A, Velamazan R, Nieto R, Navarro M *et al.* A point-of-care faecal test combining four biomarkers allows avoidance of normal colonoscopies and prioritizes symptomatic patients with a high risk of colorectal cancer. *Cancers (Basel)* 2023;**15**:721
52. Chandrapalan S, Khasawneh F, Singh B, Lewis S, Turvill J, Persaud K *et al.* A multi-centre study to risk stratify colorectal polyp surveillance patients utilising volatile organic compounds and faecal immunochemical test. *Cancers (Basel)* 2022;**14**:4951
53. Sekiguchi M, Kakugawa Y, Ikematsu H, Hotta K, Konda K, Tanaka Y *et al.* Risk stratification score improves sensitivity for advanced colorectal neoplasia in colorectal cancer screening: the Oshima study workgroup. *Clin Transl Gastroenterol* 2021;**12**:e00319
54. Farrugia A, Widlak M, Evans C, Smith SC, Arasaradnam R. Faecal immunochemical testing (FIT) in symptomatic patients: what are we missing? *Frontline Gastroenterol* 2020;**11**:28–33
55. Matter R, Marques SB, Minata MK, da Silva-Etto JMK, Sakai P, De Moura EGH. Diagnostic accuracy of one sample or two samples quantitative fecal immunochemical tests for intestinal neoplasia detection. *Arq Gastroenterol* 2020;**57**:316–322
56. Chang LC, Shun CT, Hsu WF, Tu CH, Tsai PY, Lin BR *et al.* Fecal immunochemical test detects sessile serrated adenomas and polyps with a low level of sensitivity. *Clin Gastroenterol Hepatol* 2017;**15**:872–879.e1

57. Teixeira CR. Clinical impact of the immunochemical fecal occult blood test for colorectal cancer screening in Brazil. *Ann Gastroenterol* 2017;**30**:442–445
58. Mowat C, Digby J, Strachan JA, Wilson R, Carey FA, Fraser CG *et al.* Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. *Gut* 2016;**65**:1463–1469
59. Symonds EL, Pedersen SK, Baker RT, Murray DH, Gaur S, Cole SR *et al.* A blood test for methylated BCAT1 and IKZF1 vs. a fecal immunochemical test for detection of colorectal neoplasia. *Clin Transl Gastroenterol* 2016;**7**:e137
60. Wong MCS, Ching JYL, Chan VCW, Lam TYT, Shum JP, Luk AKC *et al.* Diagnostic accuracy of a qualitative fecal immunochemical test varies with location of neoplasia but not number of specimens. *Clin Gastroenterol Hepatol* 2015;**13**:1472–1479
61. van Turenhout ST, Oort FA, van der Hulst RW, Visscher AP, Terhaar sive Droste JS, Scholten P *et al.* Prospective cross-sectional study on faecal immunochemical tests: sex specific cut-off values to obtain equal sensitivity for colorectal cancer? *BMC Gastroenterol* 2014;**14**:217
62. Chiu H, Lee Y, Tu C, Chen C, Tseng P, Liang J *et al.* Association between early-stage colon neoplasms and false-negative results from the fecal immunochemical test. *Clin Gastroenterol Hepatol* 2013;**11**:832–838.e2
63. McDonald PJ, Digby J, Innes C, Strachan JA, Carey FA, Steele RJC *et al.* Low faecal haemoglobin concentration potentially rules out significant colorectal disease. *Colorectal Disease* 2013;**15**: e151-9
64. Ou C, Kuo F, Hsu W, Lu C, Yu F, Kuo C *et al.* Comparison of the performance of guaiac-based and two immunochemical fecal occult blood tests for identifying advanced colorectal neoplasia in Taiwan. *J Dig Dis* 2013;**14**:474–483
65. Terhaar sive Droste JS, Oort FA, van der Hulst RWM, van Heukelem HA, Loffeld RJLF, van Turenhout ST *et al.* Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. *Cancer Epidemiol Biomarkers Prev* 2011;**20**:272–280
66. Terhaar sive Droste JS, van Turenhout ST, Oort FA, van der Hulst RW, Steeman VA, Coblijn U *et al.* Faecal immunochemical test accuracy in patients referred for surveillance colonoscopy: a multi-centre cohort study. *BMC Gastroenterol* 2012;**12**:94
67. Khalid-de Bakker CAJ, Jonkers DMAE, Sanduleanu S, de Bruïne AP, Meijer GA, Janssen JBMJ *et al.* Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. *Cancer Prevent Res* 2011;**4**:1563–1571
68. Rozen P, Comaneshter D, Levi Z, Hazazi R, Vilkin A, Maoz E *et al.* Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Cancer* 2010;**116**:2115–2125
69. Gimeno-García AZ, Quintero E, Nicolás-Pérez D, Hernández-Guerra M, Parra-Blanco A, Jiménez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. *Eur J Gastroenterol Hepatol* 2009;**21**:1062–1067
70. Bosch S, Bot R, Wicaksono A, Savelkoul E, van der Hulst R, Kuijvenhoven J *et al.* Early detection and follow-up of colorectal neoplasia based on faecal volatile organic compounds. *Colorectal Dis* 2020;**22**:1119–1129
71. Cheng HR, van Vorstenbosch RWR, Pachen DM, Meulen LWT, Straathof JWA, Dallinga JW *et al.* Detecting colorectal adenomas and cancer using volatile organic compounds in exhaled breath: a proof-of-principle study to improve screening. *Clin Transl Gastroenterol* 2022;**13**:e00518
72. Woodfield G, Belluomo I, Laponogov I, Veselkov K, Cross AJ, Hanna GB *et al.* Diagnostic performance of a noninvasive breath test for colorectal cancer: cOBRA1 study. *Gastroenterology* 2022; **163**:1447–1449.e8
73. Mozdiak E, Wicaksono AN, Covington JA, Arasaradnam RP. Colorectal cancer and adenoma screening using urinary volatile organic compound (VOC) detection: early results from a single-centre bowel screening population (UK BCSP). *Tech Coloproctol* 2019;**23**:343–351
74. van Keulen KE, Jansen ME, Schrauwen RWM, Kolkman JJ, Siersema PD. Volatile organic compounds in breath can serve as a non-invasive diagnostic biomarker for the detection of advanced adenomas and colorectal cancer. *Aliment Pharmacol Ther* 2020;**51**:334–346
75. Widlak MM, Neal M, Daulton E, Thomas CL, Tomkins C, Singh B *et al.* Risk stratification of symptomatic patients suspected of colorectal cancer using faecal and urinary markers. *Colorectal Dis* 2018;**20**:O335–O342
76. Amal H, Leja M, Funka K, Lasina I, Skapars R, Sivins A *et al.* Breath testing as potential colorectal cancer screening tool. *Int J Cancer* 2016;**138**:229–236
77. de Meij TG, Ben LI, van der Schee MP, Lentferink YE, Paff T, Terhaar sive Droste JS *et al.* Electronic nose can discriminate colorectal carcinoma and advanced adenomas by fecal volatile biomarker analysis: proof of principle study. *Int J Cancer* 2014; **134**:1132–1138
78. Wang H, Tso V, Wong C, Sadowski D, Fedorak RN. Development and validation of a highly sensitive urine-based test to identify patients with colonic adenomatous polyps. *Clin Transl Gastroenterol* 2014;**5**:e54
79. Vernia F, Valvano M, Fabiani S, Stefanelli G, Longo S, Viscido A *et al.* Are volatile organic compounds accurate markers in the assessment of colorectal cancer and inflammatory bowel diseases? A review. *Cancers (Basel)* 2021;**13**:2361
80. Fisher DA, Princic N, Miller-Wilson LA, Wilson K, DeYoung K, Ozbay AB *et al.* Adherence to fecal immunochemical test screening among adults at average risk for colorectal cancer. *Int J Colorectal Dis* 2022;**37**:719–721
81. NHS England. Bowel Cancer Screening Annual Report 2021 to 2022. 2024. https://www.gov.uk/government/publications/bowel-cancer-screening-annual-report-2021-to-2022/bowel-cancer-screening-annual-report-2021-to-2022. (Accessed 27 August 2024)
82. Becker R. Non-invasive cancer detection using volatile biomarkers: is urine superior to breath? *Med Hypotheses* 2020;**143**:110060
83. McFarlane M, Millard A, Hall H, Savage R, Constantinidou C, Arasaradnam R *et al.* Urinary volatile organic compounds and faecal microbiome profiles in colorectal cancer. *Colorectal Dis* 2019;**21**:1259–1269
84. Tepus M, Yau TO. Non-invasive colorectal cancer screening: an overview. *Gastrointest Tumors* 2020;**7**:62–73
85. Niedermaier T, Weigl K, Hoffmeister M, Brenner H. Fecal immunochemical tests in combination with blood tests for colorectal cancer and advanced adenoma detection—systematic review. *United Eur Gastroenterol J* 2018;**6**:13–21
86. Arasaradnam RP, McFarlane MJ, Ryan-Fisher C, Westenbrink E, Hodges P, Thomas MG *et al.* Detection of colorectal cancer (CRC) by urinary volatile organic compound analysis. *PLoS One* 2014;**9**: e108750
87. Corbacioglu Ş, Aksel G. Receiver operating characteristic curve analysis in diagnostic accuracy studies: a guide to interpreting the area under the curve value. *Turk J Emerg Med* 2023;**23**:195

88. Shaukat A, Levin TR. Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol* 2022;**19**:521–531
89. Robertson DJ, Lee JK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA *et al.* Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: a consensus statement by the US Multi-Society Task Force on colorectal cancer. *Gastroenterology* 2017;**152**:1217–1237.e3
90. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, RosenbergPS *et al.* Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst* 2017;**109**:djw322
91. Verhagen A, Hancock M. Research note: diagnostic test accuracy studies. *J Physiother* 2021;**67**:69–71
92. NHS England. National tariff payment system. 2021. https://www.england.nhs.uk/wp-content/uploads/2020/11/22-23-National-tariff-payment-system.pdf. (Accessed 26 August 2023)
93. Zhao S, Wang S, Pan P, Xia T, Chang X, Yang X *et al.* Magnitude, risk factors, and factors associated with adenoma miss rate of tandem colonoscopy: a systematic review and meta-analysis. *Gastroenterology* 2019;**156**:1661–1674.e11
94. Zhao S, Song Y, Wang S, Wang R, Feng Z, Gong A *et al.* Reduced adenoma miss rate with 9-minute vs 6-minute withdrawal times for screening colonoscopy: a multicenter randomized tandem trial. *Am J Gastroenterol* 2023;**118**:802–811