

# Systematic review with meta-analysis: volatile organic compound analysis to improve faecal immunochemical testing in the detection of colorectal cancer

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## Summary

**Background:** Faecal immunochemical test (FIT) is emerging as a valid test to rule-out the presence of colorectal cancer (CRC). However, the accuracy of FIT is dependent on the cut-off applied. An additional low-cost test could improve further detection of CRC.

**Aims:** To evaluate the efficacy of combined FIT and volatile organic compounds (VOC) in the detection of CRC within symptomatic populations.

**Methods:** Systematic reviews on the diagnostic accuracy of FIT and VOC, for the detection of CRC, were updated. Meta-analyses were performed adopting a bivariate model for sensitivity and specificity. Clinical utility of combined FIT and VOC was estimated using Fagan's nomogram. Post-test probability of FIT negatives was used as a pre-test probability for VOC.

**Results:** The pooled sensitivity and specificity of FIT at 10 µg/g faeces, for the detection of CRC, were 0.914 (95% confidence interval [CI] = 0.894-0.936) and 0.783 (CI = 0.850-0.696), respectively. For VOC, the sensitivity was 0.837 (CI = 0.781-0.881) and the specificity was 0.803 (CI = 0.870-0.712). The area under the curve for FIT and VOC were 0.926 and 0.885, respectively. In a population with 5% CRC prevalence, the estimated probability of having CRC following a negative FIT was 0.5% and following both negative FIT and VOC was 0.1%.

**Conclusions:** In a FIT-negative symptomatic population, VOC can be a good test to rule-out the presence of CRC. The estimated probability reduction by 0.4% when both tests being negative offers adequate safety netting in primary care for the exclusion of CRC. The number needed to colonoscope to identify one CRC is eight if either FIT or VOC positive. Cost-effectiveness and clinical accuracy of this approach will need further evaluation.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Yuan. The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

The complete list of authors' affiliations are listed in Appendix 1.

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## 1 | INTRODUCTION

Faecal immunochemical test (FIT) is presently used as a triage tool in the UK in symptomatic patients who are referred through the suspected cancer pathway (National Institute of Care and Excellence NG12) criteria.<sup>1</sup> The overall pooled sensitivity and specificity of FIT for the detection of CRC were 0.90 and 0.87, respectively.<sup>2</sup> Although FIT is being used in the symptomatic population as a “rule-out” test for colorectal cancer (CRC) at lower thresholds, there is still a miss rate of 1 in 10. A study, which looked at symptomatic patients referred on a 2-week referral pathway, showed that the false-negative rate of FIT—at the cut-off of 10 µg/g faeces—was 14%.<sup>3</sup> In screening populations, this could vary up to 66% depending on the cut-off values applied.<sup>4–6</sup> A false-negative FIT result can delay the diagnosis of CRC and could give false reassurance to patients. This will invariably have serious consequences not only for patients but also on the healthcare systems.

Several studies have attempted to analyse factors affecting false-negative rates of FIT. A recent systematic review and meta-analysis had identified male sex, having a family history of CRC, history of smoking, high blood glucose levels and hypertension as being significantly associated with high false-negative results.<sup>7</sup> Interestingly, a study by Ibañez-Sanz et al<sup>5</sup> concerning the diagnostic accuracy of FIT in a screening population showed that 94% of false-negative FIT values were below the limit of detection (below 4 µg/g faeces). This suggests that lowering the FIT cut-off below 10 µg/g faeces may not reduce false-negative rates significantly. Another quite recent study concluded that the sensitivity of FIT for stage I CRC was only 68% and, for stage III and IV cancers 82%–89%.<sup>8</sup> According to a recent systematic review and meta-analysis, sensitivity is even as low as 40% for T1 colorectal cancers.<sup>9</sup> In this context, introducing another test, as an adjunct to FIT, might help in improving the false-negative rates and reduce the number of cancers missed.

The detection of volatile organic compounds (VOC) emanating from bodily fluids has been shown to have a good diagnostic performance for CRC.<sup>10–13</sup> A recent meta-analysis by Zhou et al<sup>14</sup> showed that VOC had an overall sensitivity of 0.82 and specificity of 0.79 for the detection of CRC. This suggests that VOC has potential to be used as a complementary test to FIT, in particular in, the FIT-negative group.

The aim of our article was to critically assess the clinical utility of VOC in the FIT-negative symptomatic population for the detection of CRC, utilising results from two meta-analyses. This study also evaluates different scenarios (lowering FIT threshold vs adding a second test) in order to combat FIT-negative CRC. This is a collaborative effort from major centres across EU and the UK—“VOC(F)IT working group.”

## 2 | METHODOLOGY

Systematic review and meta-analyses on (1) the diagnostic performance of FIT for the detection of colorectal cancer in the

symptomatic population and (2) the diagnostic performance of VOC for the detection of CRC were carried out as described below for the purpose of this study. Both of these reviews followed the guidance laid out in the Cochrane handbook for diagnostic accuracy reviews.<sup>15</sup> Clinical utility of VOC, in this study, is defined as the diagnostic effectiveness and usefulness of VOC in the FIT-negative population.<sup>16</sup> The combination of tests refers to the analysis of VOC in the FIT-negative population in a sequential manner. All patients had a colonoscopy as a reference standard.

### 2.1 | Data sources and search strategy

#### 2.1.1 | Systematic review and meta-analysis 1: the diagnostic performance of FIT for the detection of colorectal cancer in symptomatic population

The search strategy and the eligibility criteria were described in detail elsewhere.<sup>2</sup> Literature search was re-performed using the same search strategy in Medline, EMBASE, Scopus, Cochrane and PubMed for articles published up to and including the 31st of December 2020, in order to update the systematic review. Only the articles which had looked at the FIT performance at the cut-off of 10 µg/g faeces within a symptomatic population were considered for the purpose of this meta-analysis.

#### 2.1.2 | Systematic review and meta-analysis 2: the diagnostic performance of VOC for the detection of CRC

Literature search strategies were developed using medical subject headings (MeSH) and text words related to the title. The search was performed for articles published up to and including the 31st of December 2020, using Medline, Ovid, EMBASE, Scopus and Cochrane with various combinations of keywords and subject headings—“volatile organic compounds” and “colorectal neoplasm.” The following free words were also used in combination to ensure a maximum capture (“ion mobility spectrometry,” “gas chromatography mass spectrometry,” “Field Asymmetric Ion Mobility Spectrometry,” “selected ion flow tube mass spectrometry,” “electronic nose,” “volatolome,” “metabolome”). Reference lists of included manuscripts were also checked for additional studies. The detailed search strategies for both meta-analyses are presented in the Supplementary File.

### 2.2 | Study selection

Studies were included based on the following inclusion criteria: (a) prospective and retrospective comparative cohort studies, case controlled studies, nested case-control studies, cross-sectional comparative studies and randomised controlled trials, (b) examined general adult human population of 18 years or older, (c)

published in English and were available as full texts, (d) CRC diagnosis that was made through colonoscopy, (e) studies that had reported adequate data to form  $2 \times 2$  contingency table for true positives, false positives, false negatives and true negatives and (f) for VOC—studies which evaluated VOC in both symptomatic and screening population regardless of the sampling and the analysis method used; for FIT—studies that evaluated FIT performance in symptomatic population. The exclusion criteria were as follows: (a) studies which did not have a control group and (b) studies which were published as reviews or abstracts.

## 2.3 | Quality assessment

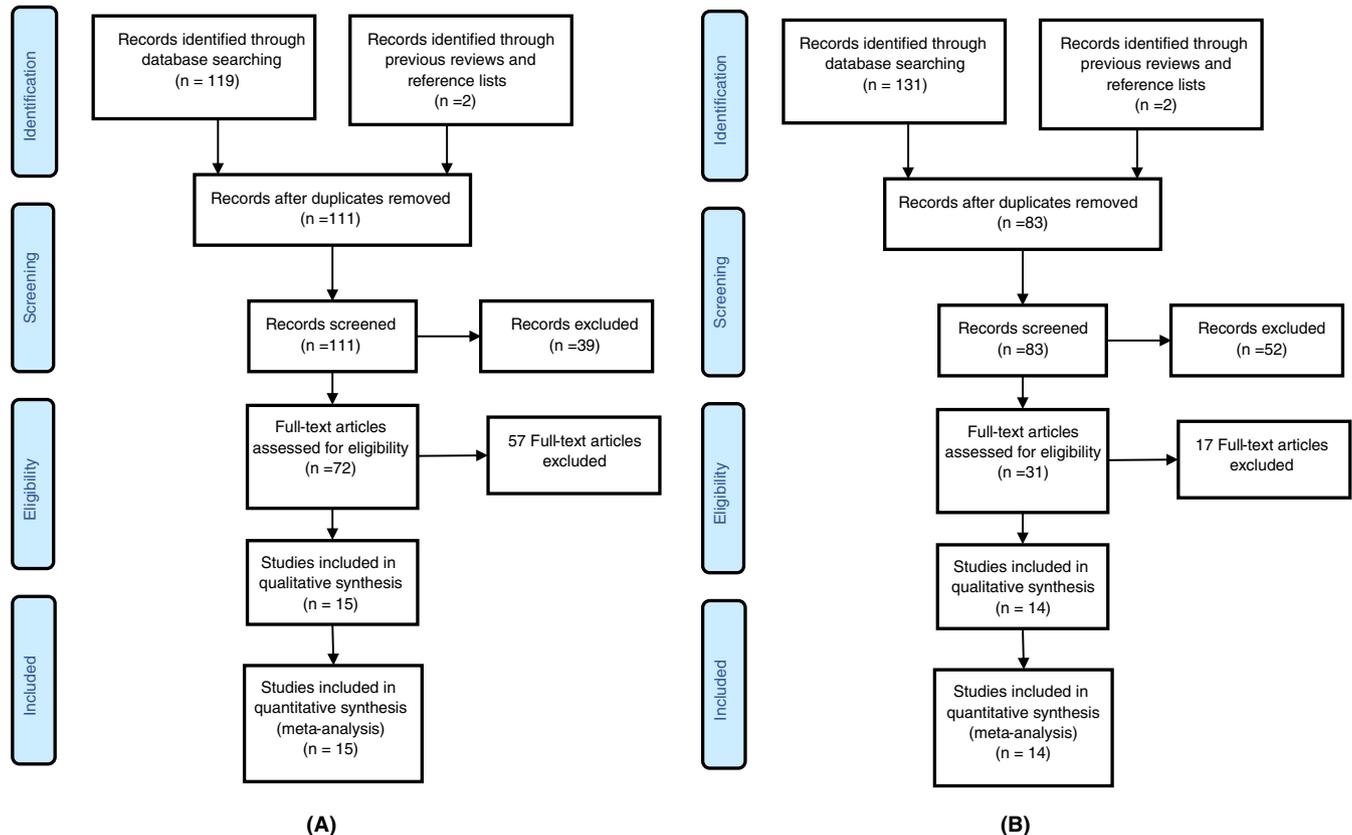
The Quadas-2 tool was used to assess the risk of bias of the included studies. The studies were assessed under four domains—patient selection, index test, reference standard and patient flow and timing; and then graded as “low risk,” “unclear” or “high risk.” Publication bias was assessed using funnel plots.

## 2.4 | Data synthesis and analysis

For both of the systematic reviews, the following data were extracted from the selected articles: authors, the year of publication, study

years, the type of sample medium used, method used for the VOC analysis, number of patients with CRC, number of healthy controls, true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN).

The R software was used for all of the statistical analysis.<sup>17</sup> If TP, TN, FP and FN were not reported explicitly, they were extracted from sensitivity and specificity and their corresponding confidence intervals or the cases used to compute them. Bivariate meta-analysis for sensitivity and specificity based on asymptotic joint distribution of sensitivity and specificity logits was performed using the package “mada” in R.<sup>18</sup> As well as individual study sensitivity and specificity and corresponding confidence intervals, forest plots used to summarise the resulted included 95% confidence intervals (CIs) from the bivariate meta-analysis. Confidence region for sensitivity and false-positive rate (1-specificity) and summary receiver operator curves (SROC) were also produced. A bivariate meta-regression analysis was performed to determine whether the VOC media and the analytical methods used contributed to the heterogeneity. Fagan's nomogram (a graphical tool for estimating how much the result on a diagnostic test changes the probability that a patient has a disease)<sup>19</sup> was used to assess the clinical utility of FIT and VOC. The prevalence of CRC in a symptomatic population was considered as a pre-test probability for the FIT nomogram and the post-test probability of CRC in a FIT-negative population was used as the pre-test probability for the VOC nomogram. Thus,



**FIGURE 1** PRISMA flow diagram showing the study selection process for (A) faecal immunochemical test and (B) volatile organic compounds

the post-test probability of CRC in both FIT- and VOC-negative population was estimated.

Number needed to scope per 1000 symptomatic patients was calculated if VOC testing is performed in FIT negatives and a comparison was made with a scenario of lowering the FIT cut-off to 2 µg/g faeces.

### 3 | RESULTS

Overall, the search had identified 121 articles for FIT and 133 articles for VOC. Among them, 15 studies<sup>20-34</sup> were included for FIT meta-analysis and 14 studies<sup>10-13,35-44</sup> for VOC meta-analysis. The selection process of the studies, for both meta-analyses, are shown

in the PRISMA diagram—Figure 1. The basic study characteristics are summarised in Tables 1 and 2.

The risk of bias assessment is summarised in Tables S1 and S2. The greatest risk of bias was identified in the flow and timing section for the studies included in FIT meta-analysis, where the duration between FIT and colonoscopy was not clearly reported. For the studies included in VOC meta-analysis, a lack of defined selection criteria and reliability of the index tests were the major contributory factors towards bias.

The funnel plots for publication bias are given in Figure S1. Deeks' regression test for funnel plot asymmetry showed an absence of publication bias among the studies included, in both FIT and VOC meta-analysis ( $P = 0.94$  and  $P = 0.43$ , respectively).

**TABLE 1** Basic characteristics of the studies for FIT in symptomatic population and their true-positive, true-negative, false-positive and false-negative rate values

Study	Country	Study year	F-Hb cut-off	Machine	True positive	True negative	False positive	False negative
Chapman et al <sup>27</sup>	UK	2019	4	OC Sensor	35	530	333	1
Cubiella et al <sup>23</sup>	Spain	2014	20	OC Sensor	85	534	156	12
Digby et al <sup>28</sup>	UK	2020	10	HM-JACKarc	25	167	268	1
D'Souza et al (a) <sup>16</sup>	UK	2020	2	HM-JACKarc	319	6157	3336	10
D'Souza et al (b) <sup>16</sup>	UK	2020	10	HM-JACKarc	299	7930	1563	30
D'Souza et al (c) <sup>16</sup>	UK	2020	150	HM-JACKarc	233	8977	516	96
Godber et al <sup>24</sup>	UK	2016	10	HM-JACKarc	11	380	116	0
Hogberg et al <sup>14</sup>	Sweden	2017	50	Actin Faecal Blood	7	246	119	1
Mcorley et al <sup>17</sup>	UK	2020	10	Many brands	252	2152	2423	14
Mowat et al <sup>15</sup>	UK	2016	10	OC Sensor	25	571	151	3
Navarro et al <sup>19</sup>	Spain	2020	10	FOB-GOLD	33	536	155	3
Nicholson et al <sup>18</sup>	UK	2020	10	HM-JACKarc	95	8943	848	10
Rodriguez-Alonso et al (a) <sup>25</sup>	Spain	2015	10	OC Sensor	29	777	196	1
Rodriguez-Alonso et al (b) <sup>25</sup>	Spain	2015	15	OC Sensor	29	809	164	1
Rodriguez-Alonso et al (c) <sup>25</sup>	Spain	2015	20	OC Sensor	28	838	135	2
Steel et al <sup>21</sup>	UK	2013	10	OC Sensor	6	257	17	0
Tehaar Sive Droste et al (a) <sup>26</sup>	Netherlands	2011	10	OC Sensor	102	1693	253	10
Tehaar Sive Droste et al (b) <sup>26</sup>	Netherlands	2011	15	OC Sensor	102	1727	219	10
Tehaar Sive Droste et al (c) <sup>26</sup>	Netherlands	2011	20	OC Sensor	101	1753	193	11
Tehaar Sive Droste et al (d) <sup>26</sup>	Netherlands	2011	30	OC Sensor	95	1788	158	17
Tehaar Sive Droste et al (e) <sup>26</sup>	Netherlands	2011	40	OC Sensor	94	1804	142	18
Tsapournas et al <sup>20</sup>	Sweden	2020	10	QuickRead go	12	177	52	1
Widlak et al <sup>22</sup>	UK	2017	7	HM-JACKarc	21	377	28	4

TABLE 2 Basic characteristics of the studies for VOC and their true-positive, true-negative, false-positive and false-negative rate values

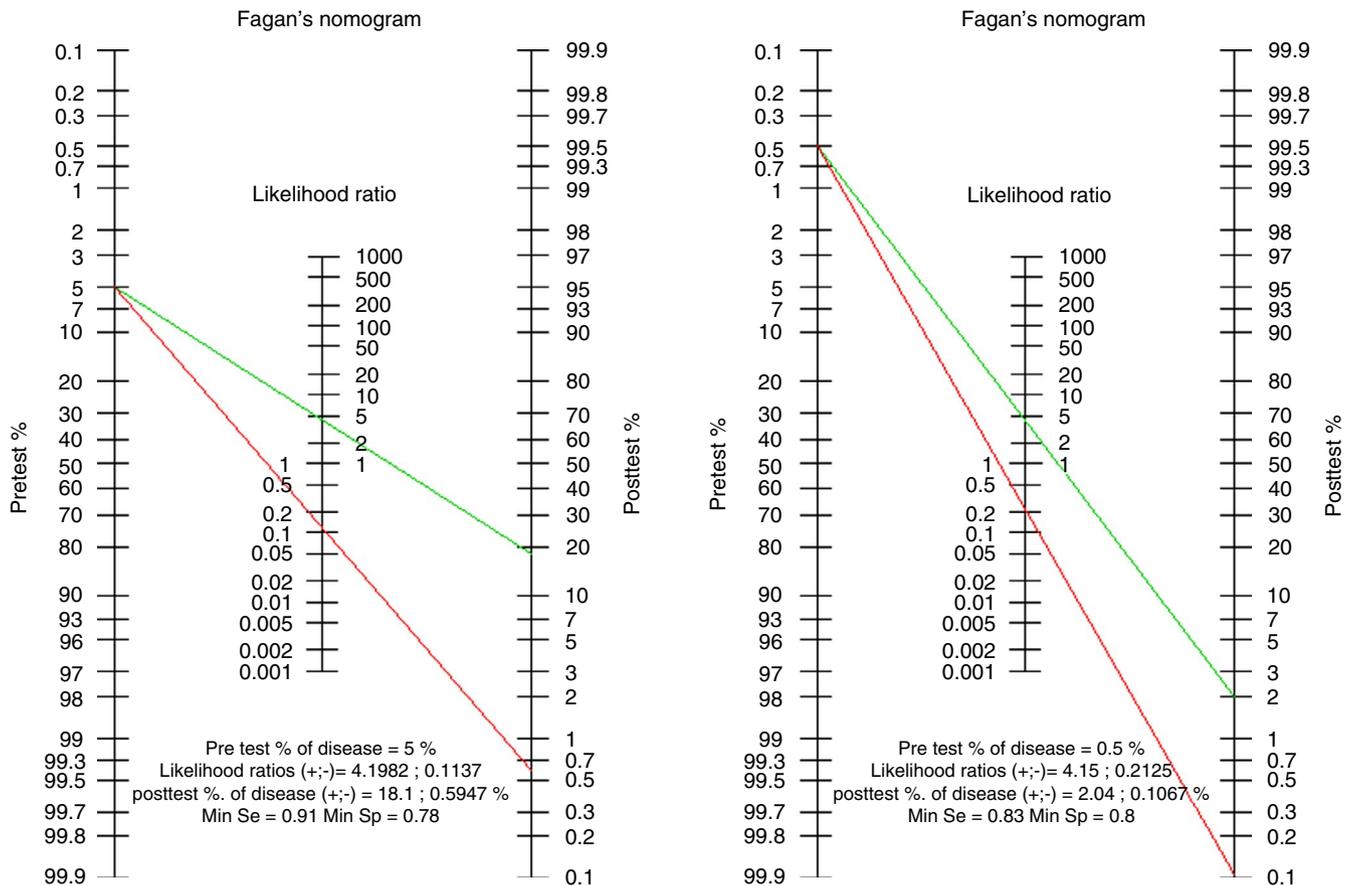
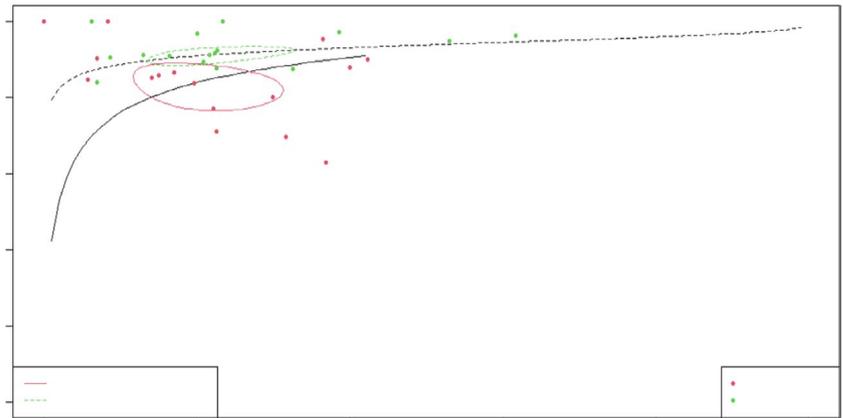
Study	Country	Year	VOC medium used	Sampler used	Sample analysis method used	No of CRC	No of controls	Stage of CRC	True positive	True negative	False positive	False negative
Altomare et al <sup>(a)</sup> <sup>8</sup>	Italy	2012	Breath	Tedlar bags	GC-MS	37	41	I-II: 19 III-IV: 18	32	34	7	5
Altomare et al <sup>(b)</sup> <sup>8</sup>	Italy	2012	Breath	Tedlar bags	GC-MS	15	10	I-II: 6 III-IV: 9	12	7	3	3
Altomare et al <sup>32</sup>	Italy	2020	Breath	ReCIVA®	GC-MS	82	87	Not reported	74	81	6	8
Amal et al <sup>11</sup>	Latvia	2015	Breath	GaSampler collection bags	e-nose	65	122	I-II: 45 III-IV: 20	55	115	7	10
Arasaradham et al <sup>34</sup>	UK	2014	Urine	Standard urine bottle	FAIMS	83	50	Not reported	73	30	20	10
Batty et al <sup>35</sup>	UK	2015	Faeces	Standard stool collection pots	SIFT-MS	31	31	Not reported	22	24	7	9
Bond et al <sup>36</sup>	UK	2018	Faeces	Standard stool collection pots	GC-MS	21	60	Not reported	18	51	9	3
Bosch et al <sup>33</sup>	Netherlands	2020	Faeces	Standard stool collection pots	GC-IMS	14	270	Not reported	14	270	0	0
de Meij et al <sup>37</sup>	Netherlands	2013	Faeces	Standard stool collection pots	e-nose	40	57	Not reported	34	49	8	6
Ishibe et al <sup>38</sup>	Japan	2017	Faecal aerosol	Tedlar bags	GC/SCD	30	26	I-II: 21 III-IV: 9	27	15	11	3
McFarlane et al <sup>9</sup>	UK	2019	Urine	Standard urine bottle	FAIMS	56	82	I-II: 25 III-IV: 29	39	56	26	17
Mozdiak et al <sup>29</sup>	UK	2019	Urine	Standard urine bottle	FAIMS	12	12	Not reported	12	11	1	0
van Keulen et al <sup>31</sup>	Netherlands	2020	Breath	Not used	e-nose	62	104	Not reported	59	66	38	3
Westenbrink et al <sup>30</sup>	UK	2014	Urine	Standard urine bottle	e-nose	39	18	Not reported	30	14	4	9
Widlak et al <sup>10</sup>	UK	2018	Urine	Standard urine bottle	FAIMS	35	233	Not reported	22	147	86	13

### 3.1 | Bivariate analysis on the diagnostic accuracy of FIT and VOC in the detection of colorectal cancer

Eleven out of fifteen studies assessed the diagnostic accuracy of FIT at the cut-off of 10 µg/g faeces. Figure 2 represents the SROC curve analysis for FIT and VOC. The pooled sensitivity and specificity of FIT at the cut-off of 10 µg/g faeces, for the detection of CRC, were

0.914 (CI = 0.894-0.936) and 0.783 (CI = 0.850-0.696), respectively. The sensitivity of VOC was 0.837 (CI = 0.781-0.881) and specificity was 0.803 (CI = 0.870-0.712). The area under the curve (AUC) for FIT was 0.926 and for VOC was 0.885. The positive and negative likelihood ratios for FIT were 4.19 and 0.11, respectively. For VOC, the positive likelihood ratio was 4.15 and the negative likelihood ratio was 0.21. The Forest plots for the sensitivity and specificity of

**FIGURE 2** Summary receiver operator curve characteristics for volatile organic compounds and faecal immunochemical test. Red and green circles indicate 95% confidence intervals for VOC and FIT, respectively. The distribution of studies for VOC and FIT are represented by red and green dots. CRC, colorectal cancer; FIT, faecal immunochemical test; VOC, volatile organic compounds



**FIGURE 3** Fagan's nomogram demonstrating the pre-test and post-test probabilities of (A) faecal immunochemical test and (B) volatile organic compounds. The post-test probability of CRC in FIT-negative group has been used as a pre-test probability for VOC. CRC, colorectal cancer; FIT, faecal immunochemical test; Min Se, Sensitivity; Min Sp, Specificity; VOC, volatile organic compounds

FIT and VOC, in the detection of CRC, are shown in Figures S2 and S3, respectively.

The test of heterogeneity suggests the presence of significant heterogeneity among the studies included in VOC meta-analysis. The covariates included in the bivariate meta-regression analysis were VOC sample media and the method of VOC analysis. The covariate sample media had three categories: breath, faeces and urine. The categories for analytical methods were gas chromatography mass spectrometry (GC/MS), gas chromatography ion mobility spectrometry (GC/IMS), field asymmetric ion mobility spectrometry (FAIMS), selected ion flow tube mass spectrometry (SIFT/MS) and electronic nose (e-nose). This led to the confirmation that the sample media and the analytical techniques contributed to heterogeneity. See Tables S3 and S4.

### 3.2 | Pre-test and post-test probabilities of CRC

The pooled positive likelihood ratio was 4.19 and the pooled negative likelihood ratio was 0.11. The prevalence of CRC in a symptomatic population is considered as 5% (pre-test probability).<sup>2,45</sup> Figure 3 illustrates the Fagan's nomograms for pre-test and post-test probabilities of CRC, following positive and negative results of FIT and VOC. The probabilities of having CRC, following a positive and negative FIT, were 18.1% and 0.5%, respectively. When the FIT-negative group was further tested for VOC, the probability of having CRC following a negative VOC test (FIT negative and VOC negative) was 0.1%.

### 3.3 | Comparison of lowering the FIT cut-off to 2 µg/g faeces vs VOC testing in FIT negatives per 1000 symptomatic patients

Table 3 presents the different scenarios in order to minimise false-negative FIT rates. The sensitivity and specificity of FIT, at the cut-off of 2 µg/g faeces, were considered as 97% and 64%,<sup>22</sup> respectively, for the calculations. At the FIT cut-off of 2 µg/g faeces, the number of cancers detected would be 48 per 1000 patients tested. The number of CRCs detected at the FIT cut-off of 10 µg/g faeces would be 45 (five CRCs missed). However, four additional cancers would be detected, if the FIT-negative group is tested with VOC. The number needed to scope in both scenarios would be eight.

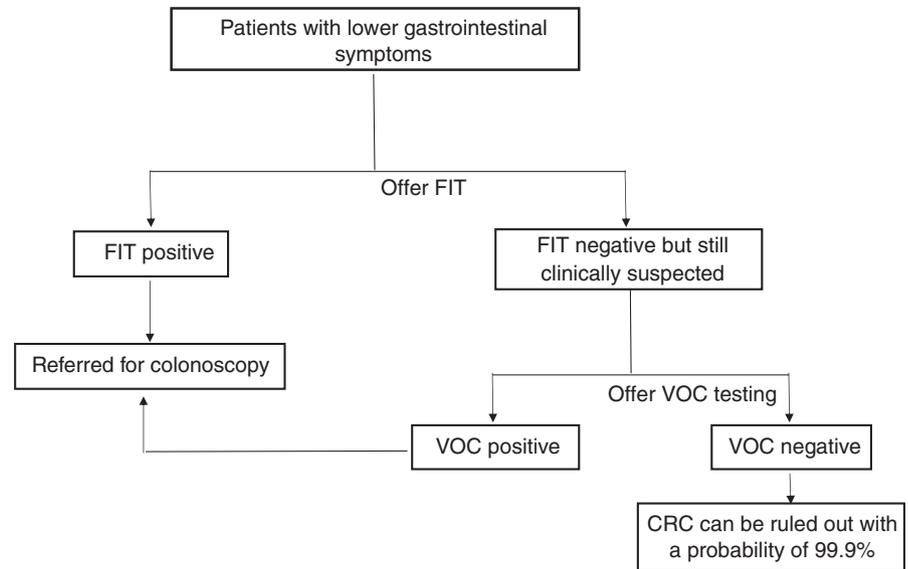
## 4 | DISCUSSION

Results of this study showed that the combination of FIT and VOC can be a better triage tool, for CRC in patients with lower gastrointestinal symptoms than FIT alone. Testing the FIT-negative group with VOC will reduce cancers missed. The combination of FIT and VOC has an overall estimated post-test probability of 0.1% for CRC in the symptomatic population, if patients had tested negative for both tests.

**TABLE 3** Number of cancers detected in patients tested positive and negative for FIT or VOC and number needed to scope to detect one cancer in different scenarios for 1000 patients tested with FIT. The prevalence of CRC in symptomatic population is considered as 5% for the calculations

	Sensitivity	Specificity	Test positives (FIT or VOC)	Test negatives (FIT or VOC)	Cancers detected among those tested positive	Cancers among those tested negative	Total colonoscopies needed	Number needed to scope to detect one CRC
<b>Scenario 1: lowering the FIT threshold to 2 µg/g faeces</b>								
At FIT cut-off of 2 µg/g faeces	97%	64%	398	602	48	2	398	8
<b>Scenario 2: VOC testing in FIT negatives (at threshold of 10 µg/g faeces)</b>								
At FIT cut-off of 10 µg/g faeces	91%	78%	254	745	45	5	254	8
If FIT negatives are to be further tested with VOC	84%	80%	152	593	4	1	152	

**FIGURE 4** A diagnostic tree approach, utilising non-invasive tests in triaging patients with symptoms for colonoscopy



The false-negative rates of the FIT could be minimised by either lowering the cut-off level or by carrying out a second test for the false-negative group. Reducing the cut-off, however, leads to high false-positive rates. D'souza et al<sup>22</sup> demonstrated that FIT had a sensitivity of 97% and a specificity of 64%, at the cut-off of 2 µg/g faeces (lowest limit of detection [LoD]). Assuming the FIT cut-off is reduced to 2 µg/g faeces, within the symptomatic population, 39.8% will have tested positive and would have required a colonoscopy. This would certainly result in higher number of unnecessary colonoscopies as well as pressure on endoscopy services. Similarly, if FIT and VOC are to be used in a sequential testing manner, 40.6% will have needed colonoscopy having tested positive for FIT or VOC test.

It is important however to consider factors which could have influenced the outcome of the above assumptions. First, the lowest limit of quantitation (LoQ) for FIT is 7 µg/g faeces. Below this level, the margin of error is high and is not recommended by manufacturers. Thus, precision estimates at a FIT threshold of 2 µg/g faeces are highly unreliable. Second, there was heterogeneity among the studies included in the meta-analysis for VOC. The heterogeneity was largely due to the sample media and the analytical methods used. Hence, the performance of VOC could be further improved, provided the sample media used and sample analysis techniques are optimised, and a universal standardised methodology is followed.<sup>46</sup> Third, certain studies included in the VOC meta-analysis had participants from both screening and symptomatic population and data could not be retrieved for the symptomatic population alone. Additionally, this estimation is based on the evidence from two separate meta-analyses for FIT and VOC and formal studies assessing FIT and VOC in pair-wise manner are required.

Patients and health commissioners might have differing views with regard to the detection of CRC in FIT-negative group and its cost burden—though minimal as urine VOC cost (estimated), for example, £25/test (€28/test). Testing with VOC is still more cost-effective than a colonoscopy or missing a case of resectable CRC. An algorithm for symptomatic patients, using non-invasive tests in

triaging referrals for colonoscopy, as depicted in Figure 4 could minimise the number of missed CRC cases.

CRC stages were not reported in all of the VOC studies; hence, diagnostic accuracy by disease staging could not be undertaken. Neidermaier et al<sup>8</sup> recently demonstrated that the FIT levels vary according to the stage of CRC, even in those with FIT under 10 µg/g faeces. The currently accepted view is that VOC is produced as a result of fermentation of non-starchy polysaccharides mediated by a complex interaction between colonic cells and microbiota.<sup>47</sup> This process is heavily influenced by external factors such as diet, smoking and medication.<sup>48</sup> Hence, it is reasonable to assume that the VOC profile would be different at different stages of CRC. Similarly, the effects of medications were not evaluated in the studies included for FIT meta-analysis.<sup>49</sup> These could have influenced the outcome of this review. Larger diagnostic accuracy studies evaluating sample media and optimising analytical methods are required. One such study is already underway (ClinicalTrials.Gov trial number 04516785).

In summary, the combination of FIT and VOC in a sequential testing manner (if negative) reduces the probability of having CRC from 0.5% to 0.1%. The number needed to colonoscope in order to identify one cancer is eight. Given the non-invasive and relatively low-cost nature of VOCs, this would seem a reasonable option though would require formal evaluation.

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#### AUTHORSHIP

*Guarantor of the article:* Ramesh P. Arasaradnam.

*Author contributions:* Chandrapalan: literature review, data collection, statistical analysis and preparation of manuscript. Kimani:

statistical guidance and manuscript editing. Bosch, Cubiella, Guardiola, Mulder, Persaud, de Meij, Altomare, Brenner, de Boer, Ricciardiello and Arasaradnam: design and concept, literature review and critical revision of the manuscript for important intellectual content. All authors have approved the final version of the manuscript.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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## APPENDIX 1

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