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Summary

Background The faecal immunochemical test (FIT) is widely employed for colorectal cancer screening. However, its sensitivity for advanced precursor lesions remains suboptimal. The multitarget FIT (mtFIT), measuring haemoglobin, calprotectin, and serpin family F member 2, has demonstrated enhanced sensitivity for advanced neoplasia, especially advanced adenomas, at equal specificity to FIT. This study aimed to prospectively validate and investigate the clinical utlility of mtFIT versus FIT in a setting of population-based colorectal cancer screening.

Methods Individuals aged 55–75 years and who were eligible for the Dutch national FIT-based colorectal cancer screening programme were invited to submit both a FIT and mtFIT sample collected from the same bowel movement. Positive FIT (47 µg/g haemoglobin cutoff) or mtFIT (based on decision-tree algorithm) led to a colonoscopy referral. The primary outcome was the relative detection rate of mtFIT versus FIT for all advanced neoplasia. Secondary outcomes were the relative detection rates of colorectal cancer, advanced adenoma, and advanced serrated polyps individually and the long-term effect of mtFIT-based versus FIT-based programmatic screening on colorectal cancer incidence, mortality, and cost, determined with microsimulation modelling. This study is registered with ClinicalTrials.gov, NCT05314309, and is complete.

Findings Between March 25 and Dec 7, 2022, 35 786 individuals were invited to participate in the study, of whom 15 283 (42·7%) consented, and 13 187 (86·3%) of 15 283 provided both mtFIT and FIT samples with valid results. Of the 13 187 participants, 6637 (50·3%) were male and 6550 (49·7%) were female. mtFIT showed a 9·11% (95% CI 8·62–9·61) positivity rate and 2·27% (95% CI 2·02–2·54) detection rate for advanced neoplasia, compared with a positivity rate of 4·08% (3·75–4·43) and a detection rate of 1·21% (1·03–1·41) for FIT. Detection rates of mtFIT versus FIT were 0·20% (95% CI 0·13–0·29) versus 0·17% (0·11–0·27) for colorectal cancer; 1·64% (1·43–1·87) versus 0·86% (0·72–1·04) for advanced adenoma, and 0·43% (0·33–0·56) versus 0·17% (0·11–0·26) for advanced serrated polyps. Modelling demonstrated that mtFIT-based screening could reduce colorectal cancer incidence by 21% and associated mortality by 18% compared with the current Dutch colorectal cancer screening programme, at feasible costs. Furthermore, at equal positivity rates, mtFIT outperformed FIT in terms of diagnostic yield. At an equally low positivity rate, mtFIT-based screening was predicted to further decrease colorectal cancer incidence by 5% and associated mortality by 4% compared with FIT-based screening.

Interpretation The higher detection rate of mtFIT for advanced adenoma compared with FIT holds the potential to translate into additional and clinically meaningful long-term colorectal cancer incidence and associated mortality reductions in programmatic colorectal cancer screening.

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Introduction

Colorectal cancer continues to pose a severe global public health challenge, emphasising the need for effective early detection strategies to improve patient outcomes.[1] Presently, the widely adopted test for colorectal cancer screening is the faecal immunochemical test (FIT), which has demonstrated effectiveness, yet holds potential for refinement.[2–4] Rather than revolutionary breakthroughs, the pragmatic path towards progress seems to lie in incremental enhancements in screening methodologies.[5]

In the pursuit of improved colorectal cancer screening techniques, various alternative molecular targets in stool, beyond proteins, have been investigated. These encompass DNA mutations, DNA promoter methylation, as well as mRNA and miRNA levels.[6,7] However, many of these approaches have not yielded the desired levels of success, possibly due to the intricate nature of the sample type, and have remained largely confined to the proof-of-concept stage. The sole exception is the multitarget stool DNA (mt-sDNA) test, which has

Research in context

Evidence before this study

We searched PubMed for publications from database inception to Oct 25, 2023, without language restrictions using the terms: "Colorectal Neoplasms", "Early Detection of Cancer", "Mass Screening", "faecal test", and "compare". This search identified 246 studies, most of which focused on the faecal occult blood test or the faecal immunochemical test (FIT). Programmatic stool-based colorectal cancer screening can reduce colorectal cancer incidence and associated mortality at the population level. The FIT that targets the human haemoglobin protein is most widely used for this purpose, but can be improved on, especially regarding the detection of high-risk precursor lesions of colorectal cancer, of which advanced adenomas are the most common. Consequently, an extensive discovery and clinical validation programme was initiated to identify distinct protein combinations measurable in stool samples to increase the efficacy of FIT. This has resulted in the multitarget FIT (mtFIT), incorporating three protein biomarkers: haemoglobin, calprotectin, and serpin family F member 2. In a retrospective analysis of a prospective colonoscopy-controlled cohort of 1284 participants, mtFIT showed a significantly higher sensitivity for advanced neoplasia than did FIT (42·9% *vs* 37·3%), while maintaining an equally high specificity of 96·6%. Particularly noteworthy, the detection of advanced adenoma was significantly increased by 35%. Implementing mtFIT in population-based colorectal cancer screening programmes could potentially decrease colorectal cancer incidence and associated mortality compared with FIT-based screening, while still being cost-effective. Moreover, the mtFIT is compatible with current screening logistics.

Added value of this study

Large interventional head-to-head studies that test clinical utility are necessary to generate evidence for implementation. To this end, in the present study mtFIT was compared with FIT in a paired-design intervention study that was conducted in the real world setting of a population-based colorectal cancer screening programme. Detection rates for advanced neoplasia, and especially advanced adenomas, were higher for mtFIT than for FIT in three different scenarios, focusing on different test positivity rates. Long-term modelling revealed that mtFIT could be cost-effective at a realistic price level and further reduce colorectal cancer incidence and associated mortality.

Implications of all the available evidence

On the basis of these findings, programmatic colorectal cancer screening could further reduce the incidence and associated mortality of this disease by using mtFIT instead of FIT.

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successfully transitioned into practical implementation.[8] Nonetheless, the utilisation of the mt-sDNA test has predominantly been limited to the USA due to its constraints in terms of cost-effectiveness and logistical feasibility, thereby rendering it unsuitable for population-based programmatic screening.[9] Notably, the diagnostic efficacy of the mt-sDNA test is also heavily reliant on the measurement of a protein, haemoglobin, in stool. Hence, protein-based methodologies appear to excel in detecting colorectal cancer screening biomarkers within the complex faecal matrix.

Consequently, about a decade ago, a comprehensive approach was initiated with the goal of identifying distinct protein combinations measurable in stool samples to increase the efficacy of FIT.[10] This discovery endeavour yielded 27 candidate proteins, from which nine were further developed, switching to antibody-based assays as opposed to mass spectrometry-based techniques, and from use of a whole bowel movement as a sample to use of a small amount of stool collected for the FIT, referred to as FIT samples.[11] This effort has resulted in the multitarget FIT (mtFIT), incorporating three protein biomarkers—haemoglobin, calprotectin, and serpin family F member 2 (alpha-2-antiplasmin, hereafter referred to as serpinF2).[11] In a colonoscopy-controlled cohort of 1284 participants, the sensitivity of mtFIT in detecting advanced neoplasia was significantly higher than for FIT (42·9% *vs* 37·3%), while maintaining an equally high specificity of 96·6%.[11] In particular, the detection of advanced adenomas was significantly increased, by 35%.[11] Early health technology assessment indicated that in population-based colorectal cancer screening programmes, mtFIT could potentially further decrease colorectal cancer incidence by 12% and mortality related to colorectal cancer by 8% compared with FIT-based screening, while still being cost-effective, up to a realistically feasible price level.[11]

In a next step towards clinical implementation of these findings, the objective of the present study was to investigate the clinical utility of mtFIT by conducting a large-scale paired-design intervention study in the setting of population-based colorectal cancer screening. Given its wide application in programmatic screening, and in compliance with the guidelines for evaluating new non-invasive colorectal cancer screening tests, FIT was used as a comparator test.[12]

Methods

Study design and participants

A prospective, paired-design, population-based intervention study for comparing mtFIT to FIT was designed in accordance with international guidelines.[12] Comprehensive methods have been previously described[13] and are also presented in the appendix (pp 1–5).

See **Online** for appendix

For logistical reasons, the national screening organisation recruited study participants from one of the five designated regions used in the national screening

programme (ie, the southwest region) that included both rural and urban areas. Participants were selected by the screening organisation to obtain a representative sample from the eligible target population of the Dutch national colorectal cancer screening programme (annually about 2 300 000 individuals). All residents fulfilling the inclusion criteria of the screening programme were eligible. The screening programme includes individuals aged 55–75 years, but excludes those who had previously had treatment for colorectal cancer, had a surveillance colonoscopy for another gastrointestinal disease, with symptoms that might be related to colorectal cancer, or with hereditary colorectal cancer.

The standard logistics of the national screening programme were employed for inviting candidate participants of the screening programme to consent for participation in the study, providing and shipping sampling devices, conducting laboratory procedures for FIT, managing data, scheduling colonoscopies, data collection, and quality management.[14] Before their scheduled regular screening invitation, selected individuals received an invitation with participant information and an informed consent form with instructions to complete and return to the coordinating centre (the Netherlands Cancer Institute, Amsterdam, Netherlands). Ethical approval was granted by the Dutch Ministry of Health, Welfare and Sport in May, 2020 (reference number 1691110-204907-PG), following recommendations from the Health Council of The Netherlands.

Procedures

After completing the informed consent form, participants received two collection tubes, instructions for sample collection (as provided by the manufacturers), a sealing bag, and a return envelope. For FIT, the FOB-Gold (Sentinel, Milan, Italy) collection tube was used, whereas for mtFIT, the OC-Sensor (Eiken Chemical, Tokyo, Japan) collection tube was used. Both samples were collected from the same bowel movement and returned by postal mail. Only individuals with valid results for both mtFIT and FIT were included in the analysis.[13]

FIT samples were measured using a fully automated clinical chemistry analyser (Bio Majesty JCA, DiaSys Diagnostic Systems, Holzheim, Germany), following the standard operating procedures of the Dutch national colorectal cancer screening programme. Quantitative FIT results for each sample were automatically transferred to the national screening database (ScreenIT; Topicus, Deventer, Netherlands), managed by the national screening organisation, and called positive or negative using the default FIT cutoff of 47 µg haemoglobin per g faeces (µg/g) used in the Dutch colorectal cancer screening programme. Despite a formal appeal, permission to use a 15 µg/g cutoff for study participants was denied by the Ministry of Health, Welfare and Sport, following recommendations from the Committee for Population Screening of the Health Council of The Netherlands.

mtFIT samples were analysed in the same laboratory as the FIT samples, using an antibody-based test that measured the concentration of the proteins haemoglobin, calprotectin, and serpinF2. The multiplex test, developed by Meso Scale Discovery (MSD, Rockville, MD, USA), employed tailored antibody assays on a proprietary electrochemiluminescence platform (appendix pp 1–2, 8).[15] Dedicated lots of the respective antibodes used in the mtFIT assay were prepared for this study and a bridging analysis was performed (appendix p 2). All samples underwent duplicate measurements with strict quality controls (appendix p 2). The mean duplicate measurements for each of the three proteins were used in the mtFIT decision tree algorithm, as previously published, for categorising the mtFIT as positive or negative (appendix pp 22–23).[11] The laboratory technicians who performed the mtFIT measurements were masked for the results of the FIT test.

Individuals who did not have a valid result for both tests (FIT and mtFIT) were excluded from the study (appendix pp 2, 6).

The national screening organisation notified participants by postal mail on the outcome of their tests, not specified by individual FIT or mtFIT results. Individuals were referred to colonoscopy if either FIT or mtFIT, or both tests were positive. Colonoscopies and histopathological evaluations were done by endoscopists and pathologists, respectively, trained and accredited for the colorectal cancer screening programme.[14,16] Both endoscopy and pathology data were collected in structured formats and entered into the central screening programme database, ScreenIT, and the Dutch Nationwide Pathology Databank, PALGA, respectively.[17] Participants were categorised on the basis of their most advanced lesion: colorectal cancer, advanced adenoma, advanced serrated polyp, non-advanced adenoma, non-advanced serrated polyp, or no colorectal neoplasia. Advanced neoplasia encompassed colorectal cancer, advanced adenoma, or advanced serrated polyp. Colorectal cancers were further categorised by location, T-stage, and N-stage, per available data. Advanced adenomas were defined as adenomas of at least 10 mm in size or with high-grade dysplasia or with at least 25% villous component. Advanced serrated polyps were serrated polyps of at least 10 mm in size or with dysplasia.

Outcomes

The primary outcome of this study was the relative detection rate of mtFIT versus FIT for advanced neoplasia. Secondary outcomes were the relative detection rates of mtFIT versus FIT for colorectal cancer, advanced adenoma, and advanced serrated polyp individually, as well as predicted long-term effects on colorectal cancer incidence, mortality, and costs for

programmatic mtFIT versus FIT-based screening. Exploratory outcomes were the relative detection rates for non-advanced adenoma, non-advanced serrated polyp, other malignancy, and no colorectal neoplasia, and the positive predictive value for advanced neoplasia. All outcomes were measured in all participants with available data.

Statistical analysis

We hypothesised that mtFIT would outperform FIT in a programmatic colorectal cancer screening setting. The sample size was based on the McNemar test for testing the difference in detection rates between mtFIT and FIT in a paired design. In 2020, the Dutch nationwide colorectal cancer screening programme reported a detection rate of 1·2% for advanced neoplasia by FIT. On the basis of our previous study, it was assumed that mtFIT would result in a relative increased detection rate of 20% at equal positivity rate.[11] Assumptions were an 80% overlap in advanced neoplasia detection between FIT and mtFIT, a two-sided significance level of 5%, and a power of 90%. This resulted in a requirement of 13 131 participants with valid study results.

Sex, age, and FIT screening history were collected for all study participants from the national colorectal cancer screening database. Race and ethnicity data are not documented in this database, and thus were not available. The positivity rate was calculated as the percentage of participants with a positive test among those with a valid test result. The detection rate was calculated as the percentage of participants with a given lesion type among those with a valid test result. Positive predictive value was calculated as the percentage of participants with advanced neoplasia among those with a positive test result. The Wilson score interval with continuity correction was used to calculate the 95% CI for detection rates and positive predictive values.

mtFIT was compared with FIT in three different scenarios: in scenario 1, the performance of mtFIT and FIT was evaluated on the basis of outcomes directly observed in the study, implying that the positivity rate of mtFIT was expected to be higher than the positivity rate of FIT, inherent to the 47 µg/g FIT cutoff mandated by the Dutch Ministry of Health, Welfare and Sport. Positivity rates in scenario 1 are based on all participants with two valid tests, irrespective of availability of complete colonoscopy data.

Subsequently, mtFIT performance was compared with FIT at equal positivity rate in two additional scenarios. Scenario 2 used equally low positivity rates for both tests, equivalent to the positivity rate of FIT at a 47 µg/g cutoff, as observed in the present study. Scenario 3 used equally high positivity rates for both tests, equivalent to the positivity rate of the mtFIT, as observed in the present study. To this end, high positivity rates for FIT were imputed using historical data as a reference. Participants without complete colonoscopy data were excluded from scenarios 2 and 3 to be able to determine detection rates, resulting in lower positivity rates in scenarios 2 and 3 than in scenario 1.

To compare mtFIT and FIT performance at equally low positivity rates (scenario 2), cutoffs for the three proteins in the mtFIT algorithm were adjusted systematically (appendix pp 2–3). The relative detection rate of this

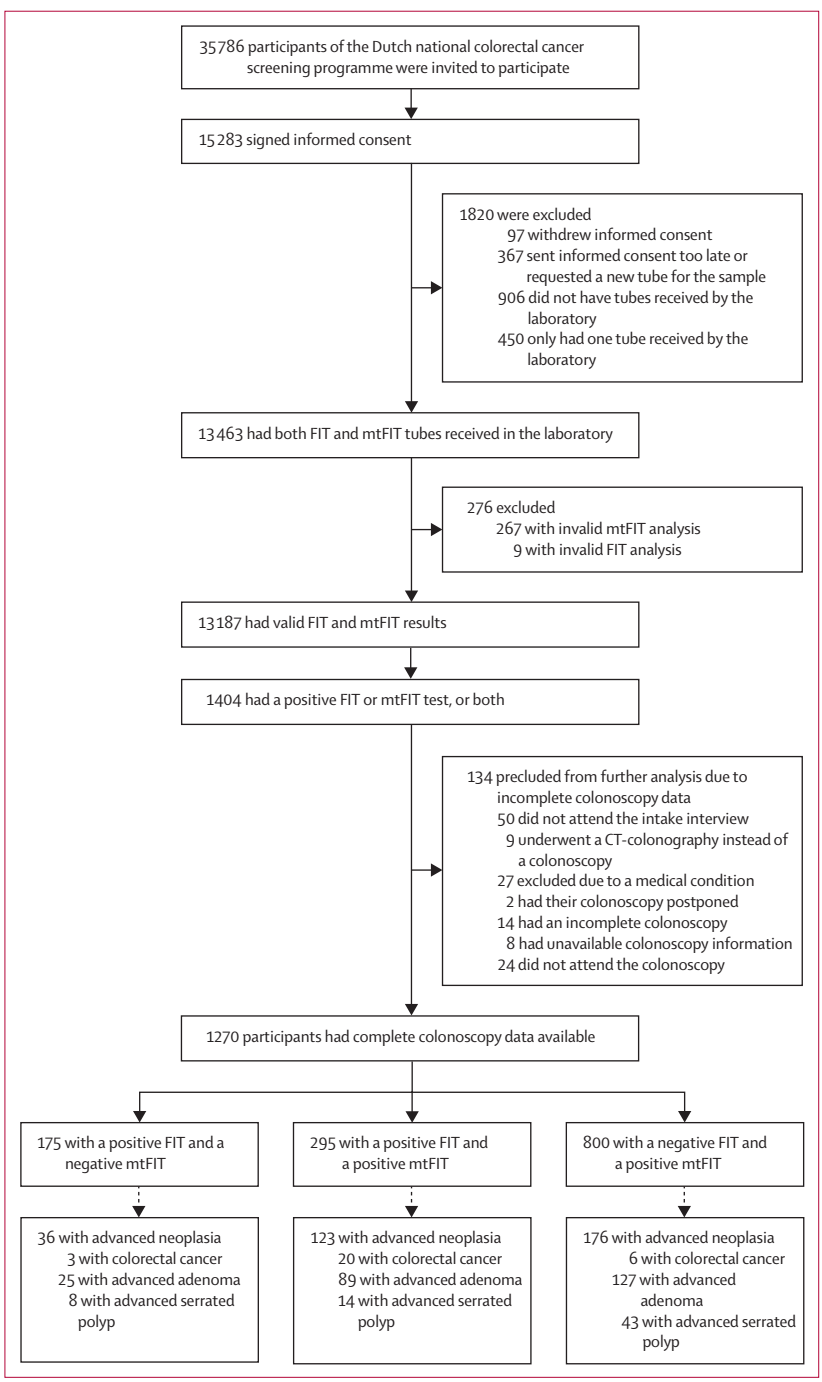


Figure 1: **Study profile**
FIT=faecal immunochemical test. mtFIT=multitarget faecal immunochemical test.

adjusted mtFIT compared with FIT was calculated, along with a 95% CI (Wald interval with Bonett-Price adjustment),[18] and tested for marginal homogeneity using a McNemar test. p values less than 0·05 were considered significant. To address over-optimism, a 10-fold cross-validation was performed, which included retraining of the cutoffs for the training sets. A cross-validated detection rate for advanced neoplasia was calculated, followed by determining the relative detection rate of mtFIT versus FIT for advanced neoplasia. Over-optimism was defined as follows: (apparent relative detection rate−cross validated relative detection rate) / cross-validated relative detection rate.

In scenario 3, mtFIT was compared with FIT at equally high positivity rate. However, using the data on detection rate at a high positivity rate from the present study would lead to bias because these were only available when colonoscopy was performed because of a positive mtFIT. As an alternative, the relative increase in advanced adenoma and colorectal cancer detection rates of FIT from low positivity rates to high positivity rates were determined with data from the colonoscopy-controlled COCOS study (n=1038) and the non-colonoscopy-controlled FIT comparison study (n=22 064) for imputation of FIT detection rates at a high positivity rate (appendix pp 3–4).[19,20] Statistical analysis was performed in R (version 4.2.2).

To evaluate the long-term effect and cost-effectiveness of programmatic mtFIT-based versus FIT-based screening, the externally validated Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) microsimulation model was used, incorporating data from the present study.[21,22] The model has been extensively described elsewhere,[21] and further details can be found in the appendix (pp 4–5).

With both tests, screening according to the Dutch national colorectal cancer screening programme was simulated, that is, biennial screening between the ages of 55 and 75 years at 73% participation (reported in 2021).[23]

Modelling was performed for scenarios 1 and 2. Modelling the long-term effect of scenario 3 was not feasible because essential input parameters for the ASCCA model (ie, detection rates for non-advanced lesions with FIT at high positivity rate, and the size of advanced adenomas) could not be obtained from the historical data used for imputation of FIT detection rates of advanced neoplasia and advanced adenoma at a high positivity rate.

Reductions in colorectal cancer incidence and associated mortality with mtFIT-based and FIT-based screening were calculated and compared. Additionally, the incremental cost-effectiveness ratio for mtFIT compared with FIT was calculated as the difference in costs divided by the difference in quality-adjusted life-years. Moreover, a threshold analysis was carried out to identify the maximum costs of mtFIT at which mtFIT-based screening remained cost-effective compared with FIT-based screening (appendix pp 4–5, 9–12). Furthermore, three sensitivity analyses were performed post hoc (appendix p 7). In brief, the first analysis assumed perfect adherence to all tests, the second assumed 10% lower costs for colonoscopy, colonoscopy complications, and colorectal cancer treatment than the costs in the main model-basis analysis, and the third assumed 10% higher costs for these clinical variables. The microsimulation was programmed in C++11. The study is registered with ClinicalTrials.gov, NCT05314309.

	Number of participants (N=13 187)	Participants with ≥1 positive test (N=1404)	Participants with complete colonoscopy data available (N=1270)
Sex			
Male	6637 (50·3%)	790 (56·3%)	718 (56·5%)
Female	6550 (49·7%)	614 (43·7%)	552 (43·5%)
Age, years			
<55	779 (5·9%)	87 (6·2%)	84 (6·6%)
55–59	2489 (18·9%)	264 (18·8%)	240 (18·9%)
60–64	3091 (23·4%)	308 (21·9%)	286 (22·5%)
65–69	3019 (22·9%)	311 (22·2%)	279 (22·0%)
70–74	3327 (25·2%)	375 (26·7%)	328 (25·8%)
≥75	482 (3·7%)	59 (4·2%)	53 (4·2%)
Number of previous FITs			
0	781 (5·9%)	88 (6·3%)	84 (6·6%)
1	1659 (12·6%)	179 (12·7%)	162 (12·8%)
2	3754 (28·5%)	381 (27·1%)	347 (27·3%)
3	2608 (19·8%)	280 (19·9%)	258 (20·3%)
4	4385 (33·3%)	476 (33·9%)	419 (33·0%)
Most advanced lesion			
Colorectal cancer	..	..	29 (2·3%)
Advanced adenoma*	..	..	241 (19·0%)
Advanced serrated polyp†	..	..	65 (5·1%)
Non-advanced adenoma	..	..	473 (37·2%)
Non-advanced serrated polyp	..	..	29 (2·3%)
Other malignancy‡	..	..	2 (0·2%)
No colorectal neoplasia§	..	..	431 (33·9%)

Data are n (%). FIT=faecal immunochemical test. *Advanced adenoma is an adenoma with at least one of the following characteristics: ≥10 mm or at least 25% villous component or high-grade dysplasia. †Advanced serrated polyp is a serrated polyp with at least one of the following characteristics: ≥10 mm or any grade of dysplasia. ‡Other malignancies were two neuroendocrine tumours (one of the rectum and one of the rectosigmoid). §Colorectal neoplasia is colorectal cancer, advanced adenoma, advanced serrated polyp, non-advanced adenoma, non-advanced serrated polyp, and other malignancy.

Table 1: **Baseline characteristics**

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 25 and Dec 7, 2022, 35 786 individuals were invited to participate in the study, of whom

15 283 (42·7%) consented to participate by signing the informed consent form. After exclusion for various reasons, including withdrawal of informed consent or samples not received by laboratory or invalid test results, 13 187 (86·3%) participants remained on the study with valid results for both FIT and mtFIT (figure 1; appendix p 6). All mtFIT and FIT analyses were performed between April 29, 2022, and March 21, 2023. The baseline characteristics of the study participants were similar to the overall Dutch colorectal cancer screening programme population with respect to sex ratio, age distribution, and distribution of the number of screening rounds in which individuals participated (table 1). Of the 13 187 participants, 6637 (50·3%) were male and 6550 (49·7%) were female. 1404 participants (10·6%) tested positive with either FIT or mtFIT, or both, and were offered a colonoscopy, complete data of which were available for 1270 (90·5%) of 1404 participants. The overlap between FIT and mtFIT detection is shown in the appendix (pp 13–14).

Of the 13 187 participants, 335 participants had advanced neoplasia (detection rate 2·54%), with 29 (8·7%) of 335 showing colorectal cancer as the most advanced lesion, 241 (71·9%) showing advanced adenoma as the most advanced lesion, and 65 (19·4%) showing advanced serrated polyps as the most advanced lesion (figure 1, table 1). Further details

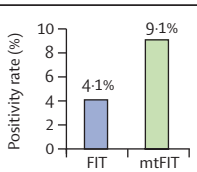
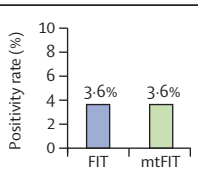
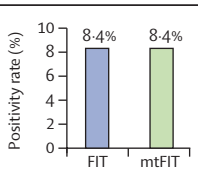
	Scenario 1: unequal positivity rates	Scenario 2: equally low positivity rates	Scenario 3: equally high positivity rates
FIT: data source	Present study	Present study	Imputed*
mtFIT: data source	Present study	Present study	Present study
FIT: cutoff (positivity rate)	47 µg/g (4·1%)	47 µg/g (3·6%)	9·6 µg/g (8·4%)
mtFIT: cutoff (positivity rate)	As previously published† (9·1%)	Adjusted‡ (3·6%)	As previously published† (8·4%)
Participants remaining for analysis	13187	13053§	13053§
Health Technology Assessment modelling	Yes	Yes	No
Positivity rates			

Figure 2: **Summaries of input parameter characteristics**

FIT=faecal immunochemical test. mtFIT=multitarget faecal immunochemical test. *Using data from two previously performed studies[19,20] with further details provided in the appendix (p 4). †As previously published.[11] ‡Further details presented in the appendix (pp 2–3). §Participants with advanced neoplasia but incomplete colonoscopies were excluded.

	FIT		mtFIT		mtFIT versus FIT	
	n	Detection rate (95% CI)	n	Detection rate (95% CI)	Relative detection rate (95% CI)*	p value*
Positive test results	538	4·08% (3·75–4·43)	1201	9·11% (8·62–9·61)	2·23	NA
Colonoscopy results	470	3·56% (3·26–3·90)	1095	8·30% (7·84–8·79)	2·33	NA
Most advanced lesion						
Advanced neoplasia†	159	1·21% (1·03–1·41)	299	2·27% (2·02–2·54)	1·88	NA
Colorectal cancer	23	0·17% (0·11–0·27)	26	0·20% (0·13–0·29)	1·13	NA
Advanced adenoma‡	114	0·86% (0·72–1·04)	216	1·64% (1·43–1·87)	1·89	NA
Advanced serrated polyp§	22	0·17% (0·11–0·26)	57	0·43% (0·33–0·56)	2·59	NA
Non-advanced adenoma	141	1·07% (0·90–1·26)	421	3·19% (2·90–3·51)	2·99	NA
Non-advanced serrated polyp	9	0·07% (0·03–0·13)	26	0·20% (0·13–0·29)	2·89	NA
Other malignancy	0	0·00% (0·00–0·04)	2	0·02% (0·00–0·06)	NA	NA
No colorectal neoplasia¶	161	1·22% (1·04–1·43)	347	2·63% (2·37–2·92)	2·16	NA

mtFIT and FIT (47 µg/g faeces) as observed in the study, N=13 187. FIT=faecal immunochemical test. mtFIT=multitarget faecal immunochemical test. NA=not applicable. *No 95% CI and p values are presented, as the rates and detection rates cannot be tested on significant differences between the mtFIT and FIT due to a different positivity rate of the tests. †Advanced neoplasia was defined as colorectal cancer, advanced adenoma, or advanced serrated polyp. ‡Advanced adenoma was defined as an adenoma with a size ≥10 mm or at least 25% villous component or high-grade dysplasia. §Advanced serrated polpy was defined as a serrated polyp ≥10 mm, with any grade of dysplasia. ¶Colorectal neoplasia is colorectal cancer, advanced adenoma, advanced serrated polyp, non-advanced adenoma, non-advanced serrated polyp, and other malignancy.

Table 2: **Detection rates per lesion type for mtFIT and FIT in scenario 1**

regarding the diagnosed colorectal cancers are in the appendix (pp 15–16). Additionally, two other malignancies were detected (one rectal neuroendocrine tumour and one rectosigmoid neuroendocrine tumour; appendix pp 13–14).

Considering detection rates of mtFIT and FIT as directly observed in the study (scenario 1), of the 13 187 participants, 1201 individuals (positivity rate 9·11% [95% CI 8·62–9·61]) tested positive with mtFIT, and 538 individuals (positivity rate 4·08% [95% CI 3·75–4·43]) tested positive with FIT (figure 2; table 2; appendix pp 13–14). Of the 13 187 participants, advanced neoplasia was detected in 299 mtFIT-positive individuals (detection rate 2·27% [95% CI 2·02–2·54]) and in 159 FIT-positive individuals (detection rate 1·21% [1·03–1·41]). Compared with FIT, mtFIT detected more colorectal cancers (26 [detection rate 0·20%; 95% CI 0·13–0·29] *vs* 23 [0·17%; 0·11–0·27]), advanced adenomas (216 [detection rate 1·64%; 1·43–1·87] *vs* 114 [0·86%; 0·72–1·04]), and advanced serrated polyps (57 [detection rate 0·43%; 0·33–0·56] *vs* 22 [0·17%; 0·11–0·26]), as well as neuroendocrine tumours (two [detection rate 0·02%; 0·00–0·06; *vs* zero [0·00; 0·00–0·04]). Positive predictive values for advanced neoplasia of mtFIT was 24·9%

	FIT		mtFIT		mtFIT versus FIT	
	n	Detection rate (95% CI)	n	Detection rate (95% CI)	Relative detection rate (95% CI)	p value
Positive test results	470	3·60% (3·29–3·94)	473	3·62% (3·31–3·96)	1·01 (0·92–1·10)	0·89
Colonoscopy results	470	3·60% (3·29–3·94)	473	3·62% (3·31–3·96)	1·01 (0·92–1·10)	0·89
Most advanced lesion						
Advanced neoplasia*	159	1·22% (1·04–1·43)	178	1·36% (1·17–1·58)	1·12 (0·99–1·27)	0·071
Colorectal cancer	23	0·18% (0·11–0·27)	22	0·17% (0·11–0·26)	0·96 (0·76–1·20)	0·71
Advanced adenoma†	114	0·87% (0·72–1·05)	133	1·02% (0·86–1·21)	1·17 (1·01–1·35)	0·039
Advanced serrated polyp‡	22	0·17% (0·11–0·26)	23	0·18% (0·11–0·27)	1·05 (0·72–1·53)	0·82
Non-advanced adenoma	141	1·08% (0·91–1·28)	160	1·23% (1·05–1·43)	1·13 (0·96–1·33)	0·13
Non-advanced serrated polyp	9	0·07% (0·03–0·14)	11	0·08% (0·04–0·16)	1·22 (0·70–2·13)	0·48
Other malignancy	0	0·00% (0·00–0·04)	0	0·00% (0·00–0·04)	NA	NA
No colorectal neoplasia§	161	1·23% (1·05–1·44)	124	0·95% (0·79–1·14)	0·77 (0·65–0·92)	0·0031

mtFIT and FIT (47 µg/g haemoglobin in faeces) at equally low positivity rate, N=13 053. FIT=faecal immunochemical test. mtFIT=multitarget faecal immunochemical test. NA=not applicable. Participants with incomplete colonoscopy data have been excluded from this analysis. *Advanced neoplasia was defined as colorectal cancer, advanced adenoma, or advanced serrated polyp. †Advanced adenoma was defined as an adenoma with a size ≥10 mm or at least 25% villous component or high-grade dysplasia. ‡Advanced serrated polpy was defined as a serrated polyp ≥10 mm, with any grade of dysplasia. §Colorectal neoplasia is colorectal cancer, advanced adenoma, advanced serrated polyp, non-advanced adenoma, non-advanced serrated polyp, and other malignancy.

Table 3: **Detection rates per lesion type for mtFIT and FIT in scenario 2**

	FIT		mtFIT		mtFIT versus FIT	
	n	Detection rate (95% CI)	n	Detection rate (95% CI)	Relative detection rate (95% CI)	p value
Positive test results	1095	8·39% (7·92–8·88)	1095	8·39% (7·92–8·88)	1·00 (0·94–1·06)	>0·99
Colonoscopy results	1095	8·39% (7·92–8·88)	1095	8·39% (7·92–8·88)	1·00 (0·94–1·06)	>0·99
Most advanced lesion						
Advanced neoplasia*	NA	1·60%†	242	1·85% (1·63–2·10)	1·15†	NA
Colorectal cancer	NA	0·22%†	26	0·20% (0·13–0·30)	0·91†	NA
Advanced adenoma‡	NA	1·38%†	216	1·65% (1·45–1·89)	1·20†	NA
Advanced serrated polyp§	NA	NA	57	0·44% (0·33–0·57)	NA	NA
Non-advanced adenoma	NA	NA	421	3·23% (2·93–3·55)	NA	NA
Non-advanced serrated polyp	NA	NA	26	0·20% (0·13–0·30)	NA	NA
Other malignancy	NA	NA	2	0·02% (0·00–0·06)	NA	NA
No colorectal neoplasia¶	NA	NA	347	2·66% (2·39–2·95)	NA	NA

mtFIT and FIT (9·6 µg/g haemoglobin in faeces) at equally high positivity rate, N=13 053. Participants with incomplete colonoscopy data have been excluded from this analysis. FIT=faecal immunochemical test. mtFIT=multitarget faecal immunochemical test. NA=not applicable. *Advanced neoplasia was defined as colorectal cancer, advanced adenoma, or advanced serrated polyp. †The detection rate for colorectal cancer and advanced adenoma was estimated on the basis of an extrapolation in a historical cohort (the FIT comparison study) of which we imputated the data in the current study. Consequently no 95% CI and p values are presented. ‡Advanced adenoma was defined as an adenoma with a size ≥10 mm or at least 25% villous component or high-grade dysplasia. §Advanced serrated polpy was defined as a serrated polyp ≥10 mm, with any grade of dysplasia. ¶Colorectal neoplasia is colorectal cancer, advanced adenoma, advanced serrated polyp, non-advanced adenoma, non-advanced serrated polyp, and other malignancy.

Table 4: **Detection rates per lesion type for mtFIT and FIT in scenario 3**

(95% CI 22·5–27·5) and for FIT was 29·6% (25·8–33·6). For each additional advanced neoplasia detected by mtFIT compared with FIT, 4·7 additional colonoscopies were required.

To compare detection rates of mtFIT and FIT at an equally low positivity rate (scenario 2), the cutoffs in the mtFIT algorithm for haemoglobin, calprotectin, and serpinF2 were adjusted (appendix pp 2–3, 23), and the FIT cutoff of 47 µg/g was retained. Excluding the 134 participants with incomplete colonoscopy data (figure 1), 13 053 participants were included in the scenario 2 analysis, among whom the mtFIT tested positive in 473 participants, and FIT tested positive in 470 participants, resulting in equal positivity rates of 3·6% for both tests (figure 2; table 3). Notably, this positivity rate differs from the 4·08% as reported in scenario 1 for FIT, because individuals with incomplete colonoscopy data have been excluded in this analysis to enable comparison of detection rates at equal positivity rate.

With mtFIT at low positivity rate, advanced neoplasia was identified in 178 of 13 053 participants (detection rate 1·36% [95% CI 1·17–1·58]), and FIT identified advanced neoplasia in 159 individuals (detection rate 1·22% [1·04–1·43]). This yielded a relative detection rate of 1·12 for advanced neoplasia (95% CI 0·99–1·27; p=0·071), with a relative detection rate of 1·10 in the 10-fold cross-validation, indicating 1·7% over-optimism. mtFIT detected significantly more advanced adenomas than did FIT (relative detection rate 1·17 [95% CI 1·01–1·35]; p=0·039). The positive predictive value for advanced neoplasia of mtFIT was 37·6% (95% CI 33·3–42·2) and for FIT was 33·8% (29·6–38·3).

For comparing detection rates of mtFIT and FIT at equally high positivity rates (scenario 3), advanced neoplasia detection rates for FIT at high positivity rate were imputed using previous Dutch FIT-based screening studies as a reference (appendix p 6, 24–26). Of the 13 053 participants using the original mtFIT algorithm, 1095 (8·39%) had a positive mtFIT and colonoscopy data available. Among these, the observed advanced neoplasia detection rate for mtFIT was 1·85% (95% CI 1·63–2·10). An imputed advanced neoplasia detection rate for FIT of 1·60% was obtained in an equally large sample of 1095 participants (8·39% positivity rate), using historical data as a reference, resulting in an estimated relative detection rate of 1·15 for mtFIT versus FIT (figure 2; table 4). Advanced neoplasia here does not include advanced serrated polyps, because the reference data did not allow for imputing detection rates for advanced serrated polyps. The positive predictive value for advanced neoplasia was estimated at 22·1% for the mtFIT and 19·9% for the FIT.

To estimate the long-term and health economic effect of mtFIT compared with FIT across multiple screening rounds, microsimulation modelling (input parameters in appendix pp 9–12, 17) for scenario 1 indicated that screening with mtFIT (at original cutoffs) compared with FIT with a cutoff of 47 µg/g was projected to reduce colorectal cancer incidence by 21% and colorectal cancer mortality by 18%, along with a 65% increase in colonoscopies (from 450 to 744 per 1000 individuals; table 5). The incremental numbers of individuals needed to scope to prevent one colorectal cancer case was 31 and to prevent one colorectal cancer death was 106. When considering a maximum mtFIT cost per test of €148, the incremental cost-effectiveness ratio of mtFIT screening remained below the willingness-to-pay threshold.

In scenario 2, at equally low positivity rates, screening with mtFIT compared with FIT was predicted to reduce colorectal cancer incidence by 5% and colorectal cancer mortality by 4%. mtFIT screening was predicted to result

	FIT (reference test; scenario 1 and 2, low positivity rate; 47 µg/g haemoglobin in faeces)	mtFIT	
		Scenario 1: high positivity rate	Scenario 2: low positivity rate
Discounted quality-adjusted life-years	16 322	16 335	16 325
Number of colonoscopies	450	744	466
Diagnostic follow-up	243	427	236
Surveillance	207	317	230
Colorectal cancer cases	46·6	37·0	44·1
Colorectal cancer incidence reduction	Reference	21%	5%
Number needed to scope to prevent one case	Reference	31	7
Colorectal cancer deaths	15·1	12·4	14·5
Colorectal cancer mortality reduction	Reference	18%	4%
Number needed to scope to prevent one death	Reference	106	26
Assumed costs mtFIT €30			
Discounted lifetime costs (×€1000)	€1650	€1645	€1631
Screening	€322	€466	€344
Surveillance colonoscopy	€127	€197	€14k
Colorectal cancer treatment	€1201	€981	€1146
Incremental cost-effectiveness ratio (€ per quality-adjusted life-year gained)	Reference	NA*	NA*
Assumed costs mtFIT €50			
Discounted lifetime costs	€1650	€1749	€1746
Screening	€322	€571	€458
Surveillance colonoscopy	€127	€197	€141
Colorectal cancer treatment	€1201	€981	€1146
Incremental cost-effectiveness ratio (€ per quality-adjusted life-years gained)	Reference	€7427	€31 848
Maximum costs per test before mtFIT screening			
Becomes more costly than FIT screening	Reference	€31	€33
Reaches willingness-to-pay threshold†	Reference	€148	€57

Presented results are absolute numbers in the lifetime of a cohort of 1000 individuals. FIT=faecal immunochemical test. mtFIT=multitarget faecal immunochemical test. NA=not applicable. *Not applicable, as mtFIT screening is less costly and more effective. †Willingness to pay threshold was set at €46 093 per quality-adjusted life-year gained.

Table 5: **Evaluation of cost-effectiveness of mtFIT versus FIT over multiple screening rounds**

in 4% more colonoscopies due to an increase in surveillance colonoscopies (appendix pp 6–7). At a maximum cost of €57 per test, the incremental cost-effectiveness ratio of mtFIT screening compared with FIT screening remained below the willingness-to-pay threshold.

In the post-hoc sensitivity analysis assuming perfect adherence to all tests and at a maximum mtFIT cost per test of €162 for scenario 1 and €68 for scenario 2, mtFIT was cost-effective compared with FIT screening (appendix pp 18–19). In the post-hoc sensitivity analyses assuming 10% lower or 10% higher costs for colonoscopy, colonoscopy complications, and colorectal cancer treatment, the maximum mtFIT cost per test stayed at approximately the same level as those in the main analysis (appendix pp 20–21).

Discussion

Various screening strategies have demonstrated the capacity to decrease the incidence and mortality of colorectal cancer.[2] Among these, FIT-based screening is globally employed, offering notable advantages such as high participation rates, user-friendliness, efficient laboratory logistics, and optimised allocation of colonoscopy resources.[24] Although FIT-based screening proves to be cost-effective compared with no screening, its limited sensitivity in detecting advanced precursor lesions requires improvement.[9] Unlike for therapeutic interventions, for diagnostic tests such as FIT and mtFIT, it is common and perfectly feasible to investigate their diagnostic accuracy head-to-head in a paired-design, or in a one-arm trial.[12] Consequently, the recently developed mtFIT was head-to-head compared with FIT in an extensive intervention trial involving 13 187 participants, run in the context of an established colorectal cancer screening programme. Trial findings confirm that mtFIT is more effective than FIT in identifying advanced adenoma and has the potential to further reduce colorectal cancer incidence and related mortality in population-based screening programmes.

As expected, the largest effect of mtFIT was shown in scenario 1, wherein mtFIT, using the previously established cutoffs, was compared with the current Dutch colorectal cancer screening programme utilising a FIT threshold of 47 µg of haemoglobin per g of faeces. Notably, mtFIT detected nearly twice the number of participants with advanced neoplasia, albeit at a substantially higher, yet still acceptable, positivity rate compared with FIT (9·11% *vs* 4·08%).[12] Because testing the null hypothesis of no difference in detection rate between mtFIT and FIT at different positivity rates would not have been rational, significance testing was omitted in this instance. In scenario 1, microsimulation modelling predicted that mtFIT-based screening would yield an extra 21% reduction in colorectal cancer incidence and an 18% reduction in mortality, compared with FIT-based screening. This equated to numbers needed to scope of 31 to avert one colorectal cancer case and 106 to prevent one associated death. Given a maximal cost per mtFIT of €148, adopting mtFIT screening remained cost-effective relative to FIT screening. Although this is a comparison at unequal positivity rates, cutoffs close to 47 µg/g or even higher are being used in daily practice in successful national colorectal cancer screening programmes including in the Netherlands, Sweden, Scotland, England, Wales, and New Zealand.[25,26] This scenario demonstrates the room for cost-effective improvement of the performance of such programmes, under the realistic assumption that the cost of mtFIT would remain below €148.

Central to the study was the comparison of mtFIT with FIT at equivalent positivity rates. However, unlike previous trials run within the setting of the Dutch national colorectal cancer screening programme, the present study had to apply the FIT threshold of 47 µg/g routinely used in the Dutch screening programme, precluding a direct comparison at the same high positivity rate.[20] As a consequence, the question of what level of incidence and mortality reduction can be achieved by lowering the FIT threshold cannot directly be answered from the data generated. Alternatively, mtFIT performance was compared with FIT at equal positivity rates in two different ways. Scenario 3, using data from previous screening, studies for imputation of FIT detection rates, revealed at a high positivity rate of both mtFIT and FIT, a 15% increase in advanced neoplasia detection rate, including colorectal cancer and advanced adenoma only, and a 20% increase in advanced adenoma detection rate compared with FIT. These differences found in scenario 3 were not tested for statistical significance since these in part were based on imputed data. Moreover, scenario 3 could not be evaluated in the microsimulation analysis, because from the imputed data, certain input variables needed for the microsimulation modelling were not available. For a direct comparison at equally low positivty rates, a recalibration of the mtFIT decision tree was needed. Despite not achieving the 20% relative increase in advanced neoplasia detection rate, which the study was powered for, a noteworthy 12% increase in advanced neoplasia detection was observed, along with a significant 17% increase in advanced adenoma detection. Although detecting 1·17 times more cases of advanced adenoma in a single screening round might not have the biggest impact on cancer incidence and mortality, this figure should be considered at the screening programme and population level. Over 11 biennial screening rounds from age 55 to age 75 years, the effect of this higher detection rate accumulates, and based on the results of microsimulation modelling, would result in an extra 5% colorectal cancer incidence reduction and 4% mortality reduction, relative to FIT-based screening with mtFIT and FIT at equivalently low positivity rates. This scenario yielded lower maximum costs than did scenario 1 for

mtFIT to be cost-effective, namely €57, which is still considered feasible for an antibody-based assay.

The present outcomes confirm findings from a previous retrospective clinical validation of mtFIT.[11] Both the potential of mtFIT to improve FIT in detecting advanced adenomas and its projected greater long-term effect on colorectal cancer incidence and associated mortality were reaffirmed, albeit with slightly reduced effect sizes, which aligns with the usual decrease in effect seen in biomarker studies at later stages of development. These findings persisted even when mtFIT cutoffs were adjusted to achieve lower positivity rates, potentially straying from the optimal cutoff range for mtFIT due to its higher sensitivity for advanced adenomas, which are more likely to shed lower quantities of target molecules.

A pivotal question would involve assessing the clinical and public health implications of these results. The swift execution of the mtFIT study, even with a non-automated research-use-only mtFIT assay, demonstrates the feasibility of incorporating mtFIT into existing FIT-based screening programmes. Microsimulation modelling emphasises the potential of mtFIT to cost-effectively decrease colorectal cancer incidence and associated mortality, a crucial factor in adoption of innovations in population-based screening. Moreover, the numbers needed to scope for averting new colorectal cancer cases or associated deaths appear acceptable and further support the adoption of mtFIT.

Given the worldwide annual colorectal cancer incidence of 1·9 million and the associated mortality of 0·9 million, even the reductions in colorectal cancer incidence (5%) and mortality (4%) observed in the low positivity rate comparison could translate into a meaningful additional reduction in colorectal cancer deaths globally every year.[1]

Notably, considering the increasingly earlier onset of colorectal cancer, the increased sensitivity of mtFIT for advanced adenomas holds particular significance, as at younger ages these lesions are the ones to be most likely encountered.[27,28] Therefore, tests with superior advanced adenoma detection rates could be particularly useful in countering early onset colorectal cancer. Furthermore, given the substantial dwell time of adenoma-to-carcinoma progression, tests with superior advanced adenoma detection rates could potentially remove the need for extending screening beyond age 75 years.

Strengths of the study encompass adherence to international guidelines for assessing new colorectal cancer screening tests and its integration within the Dutch national FIT-based colorectal cancer screening programme.[12] The study benefited from the programme's logistical, laboratory, colonoscopy, pathology, and data management infrastructure, ensuring high-quality execution.[16] The participant cohort was representative in terms of demographics, age distribution, and screening round participation. Furthermore, participants collected stool samples from a single bowel movement, which were both processed in the same laboratory. Participants and health-care providers were masked to FIT and mtFIT results. The mtFIT assay was developed in collaboration with a professional service provider under rigorous quality control.

However, a notable limitation stemmed from the Health Council of the Netherlands' decision to demand a FIT cutoff of 47 µg/g, contrasting with previous studies and preventing a direct comparison at the preferred mtFIT performance point.[20] Consequently, only an indirect comparison at equally high positivity rates (scenario 3) with historical controls was performed, which introduced a higher level of uncertainty than would have been the case in a direct comparison. This also precluded a comprehensive microsimulation analysis of the long-term effect of this scenario.

Another limitation of the study was exclusions from the study group, mostly because of events related to the complexity of combining the study logistics with the logistics of the regular screening programme, for example requesting a new collection device, which implied an automatic delivery of a standard screening packet with only a single test; or failure to return both samples to the laboratory.

Furthermore, the number of invalid test results was higher for mtFIT than FIT. This is explained by the fact that in the present study, a non-automated research-use-only mtFIT assay was used, in contrast to the industry standard clinical-grade assay used for FIT. The number of invalid test results is expected to decrease when the mtFIT also has been further developed into an automated clinical grade and industrial standard assay designed for high-throughput analyses, and to be comparable to that of the current FIT.

An intrinsic limitation of prospective studies for evaluating new cancer screening tests is that the time needed to reach the ultimate endpoint (ie, reducing death from the cancer screened for), is too long to accommodate for in the vast majority of research projects. As an alternative, intermediate endpoints, such as detection of early stage cancer or its high-risk precursor lesions, are used. The only feasible approach to still assess the potential long term clinical or public health impact of any results obtained is microsimulation modelling, as also applied in the present study. To this end, the results obtained using intermediate endpoints serve as input for modelling long-term effect. Importantly, this same modelling approach often also serves as the basis for decision making on public health policies in real world screening programmes (eg, for tuning positivity rates of screening programmes to match available colonoscopy capacity).[29] Given the important role of these models in cancer screening research, thorough validation of these models is vital. Modelling by its nature requires making assumptions on uncertain processes. Similarly, parameterising the model necessitates decisions on the evidence to include in the model (eg, on the natural history of the cancer

type screened for and the effect of interventions on outcomes). The ASCCA model used in the present study has been subjected to external validation against multiple screening trials, to cross-validation against multiple colorectal cancer screening models, and has been used in comparative modelling exercises.[22,30] Although some level of uncertainty is inherent to these models, we have demonstrated validity of the ASCCA model for inference on colorectal cancer screening strategies in the Netherlands. Although with the ASCCA model a wider range of parameters, such as screening interval, age ranges, test cutoffs, and combinations thereof, can be modelled at different values, these scenarios were considered to be beyond the scope of the present study, which merely aimed to compare the performance of mtFIT with FIT head-to-head in a real world cancer screening setting.

This study marks the final stage of a decade-long biomarker development programme, spanning discovery, retrospective validation, and now an intervention study in a screening population. Future development of mtFIT for large-scale screening extends beyond the scope of academic research. The Netherlands Cancer Institute has founded a spin-off company for further development of mtFIT into a clinical grade and industrial standard assay designed for high-throughput analyses, ready for use in large scale population-based screening programmes.

In summary, within a real-world setting of a well-established national FIT-based colorectal cancer screening programme, mtFIT exhibited superior advanced neoplasia detection compared with the standard FIT used in the Dutch colorectal cancer screening programme, albeit at a higher positivity rate. Moreover, also at equivalent positivity rates, mtFIT improved on FIT in detecting advanced adenomas. Microsimulation modelling forecasts mtFIT to reduce colorectal cancer incidence and associated mortality by at least 5% and 4%, respectively, at feasible costs. Thus, mtFIT takes incremental but meaningful and cost-effective strides beyond FIT's already substantial contribution to preventing people dying from colorectal cancer.

Contributors

PHAW, WdK, ED, MCWS, VMHC, BC, MdW, and GAM designed the study. PHAW, WdK, and FGvM-M collected data. PHAW and LM accessed and verified the underlying data. PHAW, FvW, and VMHC analysed the data. PHAW, WdK, FvW, VMHC, BC, MdW, and GAM interpreted the data. PHAW, FvW, and GAM wrote the manuscript. PHAW, FvW, GAM, WdK, FGvM-M, HEvI, LM, IH, MB, ML, MJLG, MEvL, MCWS, ED, VMHC, BC, and MdW critically revised the report for important intellectual content. All authors had access to all the data reported in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

GAM is co-founder, stockholder, and board member (Chief Scientific Officer) of CRCbioscreen BV, he has a research collaboration with CZ Health Insurances (cash contribution to ZonMW grant) and has research collaborations with Exact Sciences, Sysmex, Sentinel Ch. SpA, Personal Genome Diagnostics (PGDX), DELFi Diagnostics, and Hartwig Medical Foundation; these companies provide materials and equipment for genomic analyses. PHAW has received honorarium for consultancy from the National Institute for Public Health and the Environment. MdW is co-founder, stockholder, and board member (Chief Operations Officer) of CRCbioscreen BV. BC, MdW, VMHC, and GM have several patents pending or issued related to the work herein. MCWS has received research support from Medtronic, Boston Scientific, Sentinel, and Sysmex. ED has endoscopic equipment on loan from FujiFilm and has received a research grant from FujiFilm. ED has also received honoraria for consultancy from FujiFilm, Olympus, InterVenn, and Ambu, and speakers' fees from Olympus, GI Supply, Norgine, IPSEN, PAION, and FujiFilm. ED is also Chair CRC Screening Committee of World Endoscopy Organisation, Chair Dutch Post-polypectomy surveillance guideline committee, and Member of Post-polypectomy surveillance guideline committee of European Gastrointestinal Endoscopy. WdK received consulting fees as member of the Dutch Post-polypectomy surveillance guideline committee of European Gastrointestinal Endoscopy. All other authors declare no competing interests.

Data sharing

All the pseudonymised study data will be made available upon reasonable request to the corresponding author. To obtain access to these data, a data access request procedure must be followed in order to comply with local and international regulations.

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