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A comparative effectiveness trial of two faecal immunochemical tests for haemoglobin (FIT). Assessment of test performance and adherence in a single round of a population-based screening programme for colorectal cancer

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No of words (abstract): 258

No of words (text): 3851

No of Tables: 4

No of Figures: 0

No of References: 21

Abbreviations: AA: advanced adenoma, AN: advanced neoplasia, CI: confidence intervals, CRC: colorectal cancer, CV: coefficient of variation, DR: detection rate, EU: European Union, f-Hb: faecal haemoglobin concentration, FITTER: faecal immunochemical tests evaluation reporting, GP: general practitioner, Hb: haemoglobin, NNScope: number needed to scope to find one neoplastic lesion, PPV: positive predictive value, PR: positivity rate, RCT: randomised controlled trial, RR: relative risk

What is already known about this subject

- Faecal immunochemical tests (FIT) for haemoglobin (Hb) have been recommended as the preferred method for population colorectal cancer screening

- Several different FIT have been introduced and standardisation on faecal Hb concentration has been recommended for comparison.

- Available comparative information about diagnostic performance of different methods are mainly derived through laboratory-based studies.

What are the new findings

- The acceptability and the diagnostic performance of two FIT systems (OC-Sensor and HM-JACKarc) are similar in a screening setting.

- Diagnostic performance of FIT systems may be influenced by subject's screening history (i.e., expected prevalence of the disease).

- Setting the faecal Hb cut-off to achieve the same positivity rate with the two systems resulted in the same advanced neoplasia yield and positive predictive value,

How might it impact on clinical practice in the foreseeable future?

- Adopting faecal Hb concentration cut-offs to give equivalent positivity rates, thus using the same endoscopy resources, allows for a direct comparison of the performance of different FIT. This strategy might reduce the variability related to the individual FIT methodology, since this could alter the relationship between Hb concentration and positivity rate.

ABSTRACT

Aim: To compare acceptability and diagnostic accuracy of a recently available faecal immunochemical test (FIT) system (HM-JACKarc, Kyowa Medex Co., Ltd) with the FIT routinely used in an established screening programme (OC-Sensor, Eiken Chemical Co., Ltd).

Design: Randomised controlled trial (ISRCTN20086618) within a population-based colorectal cancer (CRC) screening programme. Subjects eligible for invitation in the Umbria Region (Italy) programme were randomised (ratio 1:1) to be screened using one of the FIT systems.

Results: Screening uptake among the 48,888 invitees was the same for both systems among subjects invited in the first round and higher with OC-Sensor than with HM-JACKarc (RR: 1.03; 95%CI: 1.02-1.04) among those invited in subsequent rounds. Positivity rate (PR) was similar with OC-Sensor (6.5%) as with HM-JACKarc (6.2%) among subjects performing their first FIT screening and higher with OC-Sensor (5.6%, RR: 1.25, 95%CI: 1.12-1.40) than with HM-JACKarc (4.4%) among those screened in previous rounds. Positive predictive value (PPV) (OC-Sensor: 25.9%, HM-JACKarc: 25.6%) and detection rate (DR) (OC-Sensor: 1.40%; HM-JACKarc: 1.42%) for advanced neoplasia (AN: CRC + advanced adenoma) were similar among subjects performing their first FIT screening. The differences in the AN PPV (OC-Sensor: 20.3%, HM-JACKarc: 22.6%) and DR (OC-Sensor: 0.96%, HM-JACKarc: 0.83%) among those screened in previous rounds were not statistically significant. The number needed to scope to detect one AN was 3.9 (95%CI: 5.8-2.9) and 3.9 (95%CI: 5.5-2.9) at first and 4.9 (95%CI: 5.8-4.2) and 4.4 (95%CI: 5.3-3.7) at subsequent screening, with OC-Sensor and HM-JACKarc respectively.

Conclusion: Our results suggest that acceptability and diagnostic performance of HM-JACKarc and of OC-Sensor systems are similar in a screening setting.

INTRODUCTION

Following the recommendation for Europe to adopt faecal immunochemical tests (FIT) for haemoglobin (Hb) as the initial non-invasive investigation of choice for population-based colorectal cancer (CRC) screening programmes[1], several different qualitative and quantitative FIT have become available for use in both screening and clinical settings. While the availability of several tests may stimulate competition, lower costs and promote technical improvements, data concerning the diagnostic performance of FIT are still mainly derived from laboratory-based evaluations[2-3], from studies conducted in clinical settings[4-6], or from studies using a paired design[7-9]. The availability of reliable information about the performance of new FIT in screening settings is crucial, however, since even relatively small variations in performance characteristics can have substantial impacts on programme organisation and delivery.

The positivity rate (PR) that personnel and financial resources can accommodate varies across regions and limited endoscopy capacity has been identified as a barrier to initiation and expansion of screening in several settings[10-11]. An increase in the number of colonoscopies resulting from a higher PR could lead, for example, to longer waiting times for assessment of participants with positive test results and this could eventually lead to in a reduction in the population invited for screening. Similarly, a reduction in the positive predictive value (PPV) can negatively affect the cost-benefit balance of a programme. Moreover, practical aspects, for example, the design and ease of use of the sample collection device can play a role when the selected population is invited to participate[2,11]. The device should be designed such that inadequate sampling or leakage are minimised. It should be easy to label with adequate information to identify the sample and it should also be suitable for packing and dispatch by normal post. The users' preferences for different devices need therefore to be assessed. Finally the costs of the system and of the postage, when relevant, need to be assessed as well [11].

Comparative effectiveness studies, conducted in the context of established CRC screening programmes, as performed in a recent study from The Netherlands,[12] may therefore represent a valuable methodology to gather the information relevant to assist screening planning and decision-making about the adoption of screening tests. We conducted a randomised controlled trial (RCT) within a population-based CRC screening programme to compare the acceptability and the diagnostic accuracy the FIT routinely used in a well-established programme (OC-Sensor, Eiken Chemical Co., Ltd, Tokyo, Japan) with a recently available automated quantitative FIT system (HM-JACKarc, Kyowa Medex Co., Ltd, Tokyo, Japan).

METHODS

The Umbria Region CRC screening programme. An organised population-based CRC screening programme was started in the Umbria Region (Italy) in 2006. All residents aged 50 to 74 years are targeted for invitation biennially and asked to collect a single faecal sample for subsequent analysis by FIT. The FIT sample collection device is mailed to the potential participants, together with a personal invitation letter signed by the appropriate general practitioner (GP), an information leaflet, the instructions for collecting and storing the sample and a pre-paid envelope for returning the device. Each device is identified by the participant's name and social security number in bar-code format. The handling of the devices, as well as the test results, is fully automated: participant's data are entered in the screening data-base using a bar-code reader by the laboratory staff when the device is processed and the results of the analytical determination of the faecal haemoglobin concentration (f-Hb) are directly recorded in the same data-base, linked to the analytical system. Subjects with a positive test result are invited by mail for a colonoscopy in one of five reference endoscopy centres, which reserve dedicated sessions for participants in the programme. The entire screening process, and treatment when necessary, are offered free of charge, following the quality standards recommended by national[13] and EU guidelines[1]. An automated linkage between the screening and pathology data-bases supports timely and comprehensive recording of all

colonoscopy and treatment results for each participant with a positive test result.

Randomization and invitation. We designed a randomized controlled trial (ISRCTN20086618) within our regional programme; the study was approved by the local Ethics Review Board (Prot. n.3032/14/AV 29/04/2014). Subjects eligible for invitation during the enrolment period (from 06 November 2014 to 31 March 2015), were randomly allocated (ratio 1:1) to be screened with one of the two FIT systems, namely, OC-Sensor and HM-JACKarc. The randomisation was stratified by gender, age group (five five-year age groups between 50 and 74 years of age), screening history (first and subsequent screening) and area of residence (urban and rural). The scheme was computer generated within the screening programme IT system and identified when individuals were to be invited to participate. The process of generating and mailing the different invitation materials was fully automated, therefore blinding the researchers to the allocation of the intervention to individuals.

Following the standard screening protocol, potential participants with a previous diagnosis of CRC (information derived from the hospital discharge records data-base), those having performed a FIT within the previous two years, or those who had a colonoscopy within the previous five years (identified from information available from the regional screening and endoscopy data-bases) and those suffering from terminal illness, or unable to provide informed consent (GP indication), were excluded from the invitation. A reminder letter was mailed to all non-responders three months following the initial invitation. The invitation kit mailed for the study included an informed consent form and a leaflet explaining the design and the rationale for the study. The invitation, containing pictorial and written materials, were designed to be as similar as possible for each of the analytical systems.

Participants were instructed to store the completed device at 4°C and to send it back to the central laboratory as soon as possible. Devices were collected and forwarded to the screening laboratory every day by the postal company, following the routine procedures of the screening programme.

Laboratory and quality control procedures. Following the Faecal Immunochemical Tests Evaluation Reporting (FITTER) guidelines, f-Hb results were reported as µg Hb/g faeces, as recommended by the Expert Working Group on FIT for Screening, the Colorectal Cancer Screening Committee, World Endoscopy Organization[14]. All analyses were performed in the central laboratory of the Umbria screening programme (National accreditation: CERMET ISO 9000:2000, ISO 9001:2008, ISO 9004:2000, UNI EN 19011:2003; D.D. n. 9628 del 21/11/2014) by three experienced laboratory medicine professionals. A detailed description of the calibration procedures and the observed analytical coefficients of variation (CV) for the two systems is available in supplement 1 (online).

The OC-Sensor device collects 10 mg faeces with a serrated probe attached to the cap into 2.0 ml buffer[2]. The cap is pushed on to the device which incorporates a small filter that removes faecal particulate matter from the sample in buffer before analysis, a feature that reduces the possibility of incorrect sampling. The analytical working range is 10-200 µg Hb/g faeces. Dilution is semi-automated after manual identification of samples with f-Hb higher than the upper analytical limit and manual replacement of the sample tube on the analyser. This dilution extends the analytical range beyond the undiluted upper analytical limit of 500 µg Hb/g faeces[2]. The HM-JACKarc device collects 2 mg of faecal material in dimples in the probe attached to the cap of the device into 2.0 ml buffer; the cap is screwed onto the sampling device. The analytical working range is 7-400 µg Hb/g faeces: the system has no automated system for automatic dilution and re-analysis of samples that have a f-Hb higher than the upper analytical limit[2].

Faecal samples were stored at 4°C in the laboratory until the time of the analysis, which was usually performed on the day of receipt and no later than the following day. An identical f-Hb cut-off criterion for referral for colonoscopy (20 µg Hb/g faeces) was used for both systems. The f-Hb results were recorded electronically and were automatically linked to the participant's record in the screening data-base.

Colonoscopy. Colonoscopy was performed in five regional reference centres using standard high-

definition endoscopes following a cathartic bowel preparation. The examination was considered complete if the caecum was visualized or, in the case of failure, when a subsequent colonoscopy, performed within the following six months, reached the caecum; the combined results of the two examinations were considered for analysis. All detected lesions were measured with open biopsy forceps and annotated according to size, morphology and localization. Histology was defined according to the World Health Organization criteria[15]: advanced adenoma (AA) was defined as an adenoma with any of the following features: size ≥10 mm, high-grade dysplasia, or villous component >20%; cancer was defined as the invasion of malignant cells beyond the muscularis mucosae.

Statistical analysis. The performance indicators considered in our comparative analysis included proportion of inadequate tests, positivity rate (PR), PPV, detection rate (DR) for CRC and AA, number needed to scope (NNScope) to detect one advanced neoplasm (AN = CRC+AA). We also compared the participation rate with the two methods, although there was no reason to expect major differences in uptake given that the two systems do not show substantial differences when characteristics such as the design and handling of the specimen collection devices possibly affecting their acceptability are considered. However, it might be that that offering a new device, albeit only slightly different from that promoted in the mass-media campaigns encouraging participation, might have some impact on the uptake.

Sample size was determined based on the expected participation rate (50%), PR (5%) and AN DR (1%), derived from the observed results of our screening programme. Based on these assumptions, enrolling 25,000 participants for each analytical system would allow detection of a 1.0%, 0.4% and 7.0% absolute difference between the two systems in positivity, AN DR and PPV, respectively, as statistically significant (α: 0.05; power: 80%). The exact method was used to calculate the 95% confidence intervals (CI) of proportions; 95% CI for the NNScope were calculate as the inverse of the 95% CI of the corresponding PPV. Relative risk (RR) with 95% CI was used as a measure of association the outcomes of interest between analytical systems, setting the OC-Sensor as the

reference system. The standardised estimates were compared using a direct standardisation method assuming the total population included in the study as the reference for calculations. All statistical tests were two-sided and a p-value of less than 0.05 was considered statistically significant.

RESULTS

During the recruitment period, 48,888 people (22,840 men and 26,048 women) were invited: 47.2% of them were living in urban areas (>150 subjects/km^2) and 52.8% in rural areas. The participation was 57.4% in the former and 63.2% in the latter. Out of the 48,888 invitees, 24,314 (11,319 men and 12,995 women) were randomised to the OC-Sensor group and 24,574 (11,521 men and 13,053 women) to the HM-JACKarc group. The two groups were comparable in age, gender and screening history (Table 1).

Participation (Table 2) was the same for both systems among individuals invited for the first time in the programme (first screening round), while it was slightly higher with OC-Sensor than with HM-JACKarc (RR: 1.03; 95%CI: 1.02-1.04) for those who had already been invited in previous rounds in the programme (subsequent screening rounds). A similar trend toward a lower participation among men than among women invited in the first screening round was observed both with OC-Sensor (RR: 0.80 (95%CI: 0.73-0.88) and with HM-JACKarc (RR: 0.83 (95%CI: 0.76-0.92); an opposite trend was observed among people having already participated in previous rounds, showing a higher participation among men than among women (OC-Sensor - RR: 1.04 (95%CI: 1.02-1.05).; HM-JACKarc - RR: 1.02 (95%CI: 1.01-1.04). Participation was higher in the youngest age group (50-54 years) for both systems at first screening and among people age 60 to 69 years as compared to younger or older age groups at subsequent screening rounds.

The overall PR (Table 3) was 6.4% (271/4247) at first and 5.0% (1240/24751) at subsequent screening and, as expected, it was higher among men than among women and increased with age quintile. Positivity was similar with OC-Sensor (6.5%) as with HM-JACKarc (6.2%, RR: 1.05, 95%CI: 0.84-1.33) at first screening, while it was higher with OC-Sensor (5.6%, RR: 1.25, 95%CI:

1.12-1.40) than with HM-JACKarc (4.4%) at subsequent screening, with a similar trend among men and women.

The uptake of colonoscopy in those with positive test results was the same (Table 3) with OC-Sensor (overall: 84.1%, men: 85.7 %, women: 82.5%) as with HM-JACKarc (overall: 83.8%, men: 83.3%, women: 84.3%), as was the completion rate of the examinations. Out of 672 subjects who undertook an assessment colonoscopy in the OC-Sensor group, 29 (4.1%) repeated the investigation within six months, following an incomplete index colonoscopy (N = 12), or to check completeness of polypectomy; similarly, in the HM-Jackarc group, 15 out of 553 (2.6%; p=0.166) repeated the investigation within six months (two following inadequate preparation and 12 to assess the site of polypectomy).

PPV for AN was similar for the two systems (OC-Sensor: 25.9%, HM-JACKarc: 25.6%) at first screening (Table 4) as it was also for the AN DR (OC-Sensor: 1.40%; HM-JACKarc: 1.42%). However, the PPV for AN at subsequent screening of a positive test result was lower with OC-Sensor (20.3%; 95%CI: 17.4%-24.1%) than with HM-JACKarc (22.6%, 95%CI: 18.9%-26.8%), but the difference did not reach the level of statistical significance. The AN DR was slightly higher, but not statistically significant, with OC-Sensor (0.96%) than with HM-JACKarc (0.83%). The NNScope to detect one case of AN was 3.9 (95%CI: 5.8-2.9) and 3.9 (95%CI: 5.5-2.9) at first screening with OC-Sensor and HM-JACKarc respectively; the corresponding figures at subsequent screening were 4.9 (95%CI: 5.8-4.2) and 4.4 (95%CI: 5.3-3.7).

Staging was available for all CRC detected at first screening both with OC-Sensor (N = 5; UICC stage: I = 4; II = 1) and with HM-JACKarc (N = 5; UICC stage: I = 2; II = 1; III = 2); staging information for CRC detected at subsequent screening was available for 11 (UICC stage: I = 7; II = 1; III = 3) out of 14 cases detected with OC-Sensor and for 15 (UICC stage: I = 9; II = 1; III = 5) out of 16 cases detected with HM-JACKarc.The proportion of CRC located in the proximal (to the descending colon) segments was 26.3% and 27.8% with OC-Sensor and HM-JACKarc respectively; the corresponding data for AN were 41.9% and 33.0%. Neither difference reached

statistical significance.

The results remained the same when considering standardised comparisons (data not shown): the PR was slightly different among participants at the initial screening test (OC-Sensor: 6.3% and HM-JACKarc: 6.6%) but the difference was not statistically significant; the crude and standardised estimates for PR, PPV and DR were the same when considering participants in subsequent screening rounds.

After increasing the f-Hb cut-off criterion for PR of OC-Sensor at subsequent screening (from 20 to 29 µg Hb/g faeces) to achieve the same PR as observed with HM-JACKarc (data not shown), the difference in the AN yield between the two methods was substantially reduced (OC Sensor: PPV: 21.0%; DR: 0.78%; NNScope: 4.8).

DISCUSSION

In a randomised controlled trial undertaken in the context of a population-based CRC screening programme, OC-Sensor and HM-JACKarc FIT analytical systems showed similar participation patterns by gender, age and screening history. The observed 3.0% increase in the participation rate with OC-Sensor among individuals having already participated in previous rounds may be related to the initial impact of a new and slightly different specimen collection device. Since all invitation kits were sent by post, following the well established procedures of the programme, individuals already used to performing the faecal sampling with the previous device might have faced difficulties in understanding the reasons for change, possibly enhancing negative attitudes to the experimental context. Importantly, those invited for their first time in the programme showed the same response with both systems, which would support this hypothesis. The lower participation found among men when compared to women across all age groups, as well as the trends for age and screening history are consistent with the results in Italian screening programmes [16].

PR, PPV and AN DR among participants undertaking their first screening were similar, while a higher PR among people with previous negative test results was observed when using the OC-Sensor as compared to the HM-JACKarc. Since the majority of participants screened after

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completion of the roll-out phase of a screening programme are expected to have already taken part in previous rounds (about 85% in the current programme), the reduction in the PR in this group will have a favourable impact on the endoscopy workload of a population based programme. The PPV for AN was also slightly decreased with OC-Sensor as compared to the HM-JACKarc, when considering subjects with previous negative test results, but the difference did not reach statistical significance, since the DR was similar for CRC, but slightly higher for AA with the OC-Sensor than with HM-JACKarc. Although the observed increase was not statistically significant, it must be realised that our study was powered to detect larger differences. Assuming that the observed increase could be declared statistically significant in a larger sample, it can be estimated that about eight additional colonoscopies would be necessary to detect one additional AN over 1,000 participants with OC-Sensor. Whether such an increase in the colonoscopy workload to achieve this small increase in the DR would be acceptable and sustainable can likely be determined only for each programme individually. Availability of such information can, however, inform a more explicit decision-making process.

Following the proposal to standardize the measuring units of f-Hb to µg Hb/g faeces,[14] to take into account the different masses of faeces collected and the volumes of the buffer in the devices, identical f-Hb cut-offs were adopted in for both systems. While similar PR and PPV were observed when using the same f-Hb cut-off among participants performing their first screening test, harmonisation of f-Hb cut-off did not result in similar PR with the two systems among subjects However, setting a higher f-Hb cut-off criterion for the PR with the OC-Sensor at subsequent rounds, to achieve the same PR with the two systems (29 µg Hb/g faeces rather than 20 µg Hb/g faeces) would result in a similar diagnostic performance. Grobbee et al.[12] have pointed out recently that comparison between FIT systems is usually done at the same f-Hb. Our findings support their thesis that improved comparison on diagnostic yield would be achieved with PR rather than f-Hb. A future publication will explore, in detail, a comparative analysis of f-Hb with the two systems, stratified by age, gender, screening history and type of lesions to test this hypothesis. The reasons

for the observed difference in the PR between the two systems at subsequent but not at first round, when using the same standardised f-Hb cut-off need to be investigated. The lower prevalence of neoplasia among people with previous negative results might result in lower average f-Hb and, for a number of reasons,[12] different methods might show different performances.

The site distribution of the screen detected lesions observed is consistent with previous reports, reflecting both the expected distribution of CRC and adenoma across colonic site, given the age distribution of our population [17] and the documented higher sensitivity of FIT for distal lesions[18] .

Conflicting data have been reported from previous studies comparing OC-Sensor and HM-JACKarc systems. In a recent Italian study [19] inviting 5044 subjects to receive both OC-Sensor and HM-JACKarc devices, after f-Hb cut-off optimisation, OC-Sensor showed a lower PR (3.5% v 6.2%) and a lower relative sensitivity for AN (73.7 v 88.2%) than HM-JACKarc. The specificity was 97.6% for the OC-Sensor and 96.0% for the HM-JACK, resulting in a decrease of the required assessments from 5.1 to 3.5% and in an estimated 30% decrease of the costs for every individual investigated for AN. On the other hand, a study comparing two cohorts screened either with OC-Sensor or HM-JACK (using the same 20 µg Hb/g faeces cut-off for positivity), in the context of a screening programme in Taiwan [20], showed a similar PR and DR for AA for both systems but a lower CRC DR and a lower interval cancer rate with OC-Sensor than with HM-JACK: however, the HM-JACK is not an identical system to the HM-JACKarc evaluated in our study. Moreover, differences in the screened populations (including baseline prevalence of disease, characteristics of the screened population with respect to gender, age and screening history) as well as in the f-Hb cut-off criteria for positivity, may explain the observed findings in the Taiwan study [18]. These studies do suggest that, even when using a standardized reporting unit system, identical f-Hb may perform differently between systems, while the choice of a suitable f-Hb cut-off for positivity in a population-based screening setting should take into account also the PR, influencing the colonoscopy workload. Our results, showing a similar diagnostic performance of the two systems,

may not be directly comparable with the findings from previous reports, since updated systems were used both for OC Sensor (different buffer) and for HM-JACKarc (different analytical system, collection device and analytical range to the HM-JACK system). They would support, however, the conclusion of the Taiwan study suggesting that differences in diagnostic performance may still be expected, despite harmonisation of f-Hb cut-off.

One of the main strengths of our study is that it was conducted in standard care conditions, within an established population-based CRC screening programme, targeting both men and women with different screening histories over the entire screening age range. It can therefore provide relevant indications about the expected impact of the adoption of these systems in an average risk population both at first and subsequent screening. The compliance with colonoscopy referral among subjects with positive screening test results and the colonoscopy completion rate were similar in the two groups: they were higher than the average level of these indicators in Italian programmes and consistent with the results of the regional programme in the more recent years. [16] The high quality of the assessment procedures reinforces the validity of our conclusions.

In conclusion, our results would suggest that acceptability and diagnostic performance characteristics of the OC-Sensor and the newer HM-JACKarc systems are similar in a screening setting. The roll-out of programmes and the availability of endoscopy resources should be considered when choosing the f-Hb cut-off criterion for positivity of a FIT system for CRC screening. Selection of the same harmonised f-Hb cut-off may still result in different PR and PPV for AN. Adopting f-Hb cut-offs to give equivalent PR allows instead for a direct comparison of the performance of different systems when using the same amount of endoscopy resources. Using PR as a reference might also reduce the variation possibly related to ongoing technical developments of the specimen collection devices (of the buffer in particular) introduced by manufacturers. A recent study, for example, showed that a change in the formulation of the OC-Sensor device buffer, aimed at stabilising the Hb in the samples and reducing Hb degradation, was associated with higher f-Hb for values below the threshold of 20 μg Hb/g faeces compared with the old buffer[21]. Although the

difference in the PR observed in that study was not statistically significant, different buffer

formulations, and other factors, might alter the relationship between Hb concentration and PR.

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Patient consent: Obtained.

Ethics approval: The study was approved by the local Ethics Review Board Prot. n.3032/14/AV

29/04/2014

Provenance and peer review Not commissioned; externally peer reviewed.

Table 1   **Characteristics of participants**
by FIT system, gender, age and screening history

First screening	OC-Sensor			HM-JACKarc		
Age (years)	Men N (%)	Women N (%)	Total N (%)*	Men N (%)	Women N (%)	Total N (%)*
50-54	2084	2187	4271	2188	2123	4311
	48.8	51.2	77.6	50.8	49.2	77.2
55-59	586	590	1176	561	620	1181
	49.8	50.2	33.3	47.5	52.5	32.5
60-64	687	656	1343	657	679	1336
	51.2	48.8	22.8	49.2	50.8	22.7
65-69	1026	1075	2101	1052	1009	2061
	48.8	51.2	36.6	51.0	49.0	35.6
70-74	416	441	857	399	463	862
	48.5	51.5	23.5	46.3	53.7	23.4
Total	4799	4949	9748	4857	4894	9751
	49.2	50.8	40.1	49.8	50.2	39.7
Subsequent screening	OC-Sensor			HM-JACKarc		
Age (years)	Men N (%)	Women N (%)	Total N (%)**	Men N (%)	Women N (%)	Total N (%)**
50-54	541	695	1236	577	697	1274
	43.8	56.2	22.4	45.3	54.7	22.8
55-59	1052	1300	2352	1078	1376	2454
	44.7	55.3	66.7	43.9	56.1	67.5
60-64	2045	2512	4557	1994	2547	4541
	44.9	55.1	77.2	43.9	56.1	77.3
65-69	1625	2007	3632	1712	2021	3733
	44.7	55.3	63.4	45.9	54.1	64.4
70-74	1257	1532	2789	1303	1518	2821
	45.1	54.9	76.5	46.2	53.8	76.6
Total	6520	8046	14566	6664	8159	14823
	44.8	55.2	59.9	45.0	55.0	60.3
Total	OC-Sensor			HM-JACKarc		
Age (years)	Men N (%)	Women N (%)	Total N (%)	Men N (%)	Women N (%)	Total N (%)
50-54	2625	2882	5507	2765	2820	5585
	47.7	52.3	22.6	49.5	50.5	22.7
55-59	1638	1890	3528	1639	1996	3635
	46.4	53.6	14.5	45.1	54.9	14.8
60-64	2732	3168	5900	2651	3226	5877
	46.3	53.7	24.3	45.1	54.9	23.9
65-69	2651	3082	5733	2764	3030	5794
	46.2	53.8	23.6	47.7	52.3	23.6
70-74	1673	1973	3646	1702	1981	3683
	45.9	54.1	15.0	46.2	53.8	15.0
Total	11319	12995	24314	11521	13053	24574
	46.6	53.4		46.9	53.1	

* percentage of subjects in the first screening round out of those in the age group
** percentage of subjects in the subsequent screening rounds out of those in the age group

& Distribution of N of previous tests: OC-Sensor: 1=17.0%; 2=28.9%; 3=26.3%; 4=26.3%; 5=1.5%
HM-JACKarc: 1=17.1%; 2=29.1%; 3=26.4%; 4=26.2%; 5=1.2%

Table 2.   Uptake of the screening invitation with the OC-Sensor and HM-JACKarc systems by gender, age and screening history

OC-Sensor – first screening

Age (years)	Men Invited	Men Uptake N	Men Uptake %	Women Invited	Women Uptake N	Women Uptake %	Total Invited	Total Uptake N	Total Uptake %
50-54	2084	560	26.9	2187	808	36.9	4271	1368	32.0
55-59	586	97	16.6	590	99	16.8	1176	196	16.7
60-64	687	101	14.7	656	76	11.6	1343	177	13.2
65-69	1026	133	13.0	1075	124	11.5	2101	257	12.2
70-74	416	69	16.6	441	71	16.1	857	140	16.3
Total	**4799**	**960**	**20.0**	**4949**	**1178**	**23.8**	**9748**	**2138**	**21.9**

HM-JACKarc – first screeing

Age (years)	Men Invited	Men Uptake N	Men Uptake %	Women Invited	Women Uptake N	Women Uptake %	Total Invited	Total Uptake N	Total Uptake %
50-54	2188	659	30.1	2123	771	36.3	4311	1430	33.2
55-59	561	91	16.2	620	88	14.2	1181	179	15.2
60-64	657	75	11.4	679	114	16.8	1336	189	14.1
65-69	1052	101	9.6	1009	109	10.8	2061	210	10.2
70-74	399	49	12.3	463	52	11.2	862	101	11.7
Total	**4857**	**975**	**20.1**	**4894**	**1134**	**23.2**	**9751**	**2109**	**21.6**

OC-Sensor – subsequent screening

Age (years)	Men Invited	Men Uptake N	Men Uptake %	Women Invited	Women Uptake N	Women Uptake %	Total Invited	Total Uptake N	Total Uptake %
50-54	541	440	81.3	695	575	82.7	1236	1015	82.1
55-59	1052	860	81.7	1300	1050	80.8	2352	1910	81.2
60-64	2045	1844	90.2	2512	2198	87.5	4557	4042	88.7
65-69	1625	1452	89.4	2007	1703	84.9	3632	3155	86.9
70-74	1257	1091	86.8	1532	1231	80.4	2789	2322	83.3
Total *	**6520**	**5687**	**87.2**	**8046**	**6757**	**84.0**	**14566**	**12444**	**85.4**

HM-JACKarc – subsequent screening

Age (years)	Men Invited	Men Uptake N	Men Uptake %	Women Invited	Women Uptake N	Women Uptake %	Total Invited	Total Uptake N	Total Uptake %
50-54	577	457	79.2	697	565	81.1	1274	1022	80.2
55-59	1078	876	81.3	1376	1102	80.1	2454	1978	80.6
60-64	1994	1692	84.9	2547	2162	84.9	4541	3854	84.9
65-69	1712	1467	85.7	2021	1687	83.5	3733	3154	84.5
70-74	1303	1109	85.1	1518	1190	78.4	2821	2299	81.5
Total *	**6664**	**5601**	**84.0**	**8159**	**6706**	**82.2**	**14823**	**12307**	**83.0**

* RR - OC-Sensor vs HM-JACKarc: 1.03 (95%CI: 1.02-1.04).

Table 3: **Positivity and colonoscopy performed and completed**
for OC-Sensor and HM-JACKarc systems by gender, age and screening history

OC-Sensor – Men - first screening

Age (years)	Examined	FIT positive		Colonoscopy performed		Colonoscopy completed	
		N	%	N	%	N	%
50-54	560	30	5.4	28	93.3	26	92.9
55-59	97	8	8.2	6	75.0	5	83.3
60-64	101	9	8.9	7	77.8	7	100.0
65-69	133	13	9.8	9	69.2	9	100.0
70-74	69	14	20.3	13	92.9	12	92.3
Total	960	74	7.7	63	85.1	59	93.7

OC-Sensor – Women - first screening

Age (years)	Examined	FIT positive		Colonoscopy performed		Colonoscopy completed	
		N	%	N	%	N	%
50-54	808	30	3.7	28	93.3	25	89.3
55-59	99	3	3.0	3	100.0	3	100.0
60-64	76	5	6.6	4	80.0	4	100.0
65-69	124	9	7.3	4	44.4	2	50.0
70-74	71	19	26.8	14	73.7	13	92.9
Total	1178	66	5.6	53	80.3	47	88.7

OC-Sensor – Total - first screening

Age (years)	Examined	FIT positive*		Colonoscopy performed *		Colonoscopy completed *	
		N	%	N	%	N	%
50-54	1368	60	4.4	56	93.3	51	91.1
55-59	196	11	5.6	9	81.8	8	88.9
60-64	177	14	7.9	11	78.6	11	100.0
65-69	257	22	8.6	13	59.1	11	84.6
70-74	140	33	23.6	27	81.8	25	92.6
Total	2138	140	6.5	116	82.9	106	91.4

HM-JACKarc – Men - first screening

Age (years)	Examined	FIT positive		Colonoscopy performed		Colonoscopy completed	
		N	%	N	%	N	%
50-54	659	25	3.8	24	96.0	24	100.0
55-59	91	6	6.6	4	66.7	4	100.0
60-64	75	7	9.3	7	100.0	7	100.0
65-69	101	11	10.9	8	72.7	7	87.5
70-74	49	30	61.2	27	90.0	27	100.0
Total	975	79	8.1	70	88.6	69	98.6

HM-JACKarc – Women - first screening

Age (years)	Examined	FIT positive		Colonoscopy performed		Colonosocpy completed	
		N	%	N	%	N	%
50-54	771	21	2.7	18	85.7	17	94.4
55-59	88	1	1.1	1	100.0	1	100.0
60-64	114	9	7.9	8	88.9	7	87.5
65-69	109	9	8.3	8	88.9	7	87.5
70-74	52	12	23.1	12	100.0	11	91.7
Total	1134	52	4.6	47	90.4	43	91.5

HM-JACKarc - Total – first screening

Age (years)	Examined	FIT positive *		Colonoscopy performed *		Colonoscopy completed *	
		N	%	N	%	N	%
50-54	1430	46	3.2	42	91.3	41	97.6
55-59	179	7	3.9	5	71.4	5	100.0
60-64	189	16	8.5	15	93.8	14	93.3
65-69	210	20	9.5	16	80.0	14	87.5
70-74	101	42	41.6	39	92.9	38	97.4
Total	2109	131	6.2	117	89.3	112	95.7

* **p (**OC-Sensor vs HM-JACKarc **)** = NS

OC-Sensor – Men – subsequent screening

Age (years)	Examined	FIT positive N		Colonoscopy performed N		Colonoscopy completed N	
50-54	440	23	5.2	20	87.0	20	100.0
55-59	860	39	4.5	35	89.7	34	97.1
60-64	1844	102	5.5	93	91.2	88	94.6
65-69	1452	95	6.5	81	85.3	77	95.1
70-74	1091	100	9.2	79	79.0	75	94.9
Total	5687	359	6.3	308	85.8	294	95.5

OC-Sensor – Women – subsequent screening

Age (years)	Examined	FIT positive N		Colonoscopy performed N		Colonoscopy completed N	
50-54	575	25	4.3	21	84.0	19	90.5
55-59	1050	40	3.8	28	70.0	28	100.0
60-64	2198	86	3.9	77	89.5	73	94.8
65-69	1703	101	5.9	85	84.2	81	95.3
70-74	1231	82	6.7	66	80.5	63	95.5
Total	6757	334	4.9	277	82.9	264	95.3

OC-Sensor – Total –- subsequent screening

Age (years)	Examined	FIT positive ** N		Colonoscopy performed * N		Colonoscopy completed * N	
50-54	1015	48	4.7	41	85.4	39	95.1
55-59	1910	79	4.1	63	79.7	62	98.4
60-64	4042	188	4.7	170	90.4	161	94.7
65-69	3155	196	6.2	166	84.7	158	95.2
70-74	2322	182	7.8	145	79.7	138	95.2
Total	12444	693	5.6	585	84.4	558	95.4

HM-JACKarc – Men – subsequent screening

Age (years)	Examined	FIT positive N		Colonoscopy performed N		Colonoscopy completed N	
50-54	457	16	3.5	8	50.0	8	100.0
55-59	876	37	4.2	34	91.9	33	97.1
60-64	1692	74	4.4	64	86.5	63	98.4
65-69	1467	85	5.8	72	84.7	71	98.6
70-74	1109	75	6.8	57	76.0	56	98.2
Total	5601	287	5.1	235	81.9	231	98.3

HM-JACKarc- Women -– subsequent screening

Age (years	Examined	FIT + N		Colonoscopy performed N		Colonoscopy completed N	
50-54	565	16	2.8	14	87.5	14	100.0
55-59	1102	34	3.1	28	82.4	27	96.4
60-64	2162	73	3.4	64	87.7	61	95.3
65-69	1687	64	3.8	57	89.1	55	96.5
70-74	1190	73	6.1	53	72.6	52	98.1
Total	6706	260	3.9	216	83.1	209	96.8

HM-JACKarc – Total – subsequent screening

Age (years)	Examined	FIT positive ** N		Colonoscopy performed * N		Colonoscopy completed * N	
50-54	1022	32	3.1	22	68.8	22	100.0
55-59	1978	71	3.6	62	87.3	60	96.8
60-64	3854	147	3.8	128	87.1	124	96.9
65-69	3154	149	4.7	129	86.6	126	97.7
70-74	2299	148	6.4	110	74.3	108	98.2
Total	12307	547	4.4	451	82.4	440	97.6

* p (OC-Sensor vs HM-JACKarc) = NS
** RR - OC-Sensor vs HM-JACKarc: 1.25 (95%CI: 1.12-1.40).

Table 4. **Detection rate and positive predictive value (PPV) for advanced adenoma and CRC by gender, age and screening history**

OC-Sensor - Men - first screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	Advanced adenoma %	CRC N	CRC %	PPV AN N
50-54	5.4	28	6	1.1	0	0.00	21.4
55-59	8.2	6	2	2.1	0	0.00	33.3
60-64	8.9	7	4	4.0	0	0.00	57.1
65-69	9.8	9	2	1.5	1	0.75	33.3
70-74	20.3	13	3	4.4	1	1.45	30.8
Total	7.7	63	17	1.8	2	0.21	30.2

OC-Sensor - Women - first screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	Advanced adenoma %	CRC N	CRC %	PPV AN N
50-54	3.7	28	6	0.74	0	0.00	21.4
55-59	3.0	3	0	0.00	0	0.00	0.0
60-64	6.6	4	0	0.00	1	1.32	25.0
65-69	7.3	4	0	0.00	1	0.81	25.0
70-74	26.8	14	2	2.82	1	1.41	21.4
Total	5.6	53	8	0.68	3	0.25	20.8

OC-Sensor - Total - first screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	Advanced adenoma %	CRC * N	CRC * %	PPV AN * N
50-54	4.4	56	12	0.88	0	0.00	21.4
55-59	5.6	9	2	1.02	0	0.00	22.2
60-64	7.9	11	4	2.26	1	0.56	45.5
65-69	8.6	13	2	0.78	2	0.78	30.8
70-74	23.6	27	5	3.57	2	1.43	25.9
Total	6.5	116	25	1.17	5	0.23	25.9

HM-JACKarc - Men - first screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	Advanced adenoma %	CRC N	CRC %	PPV AN N
50-54	3.8	24	4	0.61	2	0.30	25.0
55-59	6.6	4	1	1.10	0	0.00	25.0
60-64	9.3	7	0	0.00	0	0.00	0.0
65-69	10.9	8	5	4.95	0	0.00	62.5
70-74	61.2	27	7	14.29	1	2.04	29.6
Total	8.1	70	17	1.74	3	0.31	28.6

HM-JACKarc - Women - first screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	Advanced adenoma %	CRC N	CRC %	PPV AN N
50-54	2.7	18	4	0.52	2	0.26	33.3
55-59	1.1	1	0	0.00	0	0.00	0.0
60-64	7.9	8	2	1.75	0	0.00	25.0
65-69	8.3	8	1	0.92	0	0.00	12.5
70-74	23.1	12	1	1.92	0	0.00	8.3
Total	4.6	47	8	0.71	2	0.18	21.3

HM-JACKarc - Total- first screening-

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	Advanced adenoma %	CRC * N	CRC * %	PPV AN * %
50-54	3.2	42	8	0.6	4	0.28	28.6
55-59	3.9	5	1	0.6	0	0.00	20.0
60-64	8.5	15	2	1.1	0	0.00	13.3
65-69	9.5	16	6	2.9	0	0.00	37.5
70-74	41.6	39	8	7.9	1	0.99	23.1
Total	6.2	117	25	1.2	5	0.24	25.6

* p (OC-Sensor vs HM-JACKarc **)** = NS

OC-Sensor - Men - subsequent screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	%	CRC N	%	PPV AN N
50-54	5.2	20	3	0.7	0	0.00	15.0
55-59	4.5	35	3	0.4	0	0.00	8.6
60-64	5.5	93	16	0.89	2	0.11	19.4
65-69	6.5	81	17	1.2	3	0.21	24.7
70-74	9.2	79	17	1.6	2	0.18	24.1
Total	6.3	308	56	1.0	7	0.12	20.5

OC-Sensor - Women - subsequent screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	%	CRC N	%	PPV AN N
50-54	4.3	21	3	0.5	1	0.17	19.1
55-59	3.8	28	3	0.3	0	0.00	10.7
60-64	3.9	77	16	0.7	3	0.14	24.7
65-69	5.9	85	13	0.8	2	0.12	17.7
70-74	6.7	66	14	1.1	1	0.08	22.7
Total	4.9	277	49	0.7	7	0.10	20.2

OC-Sensor - Total - subsequent screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma * N	%	CRC * N	%	PPV AN * N
50-54	4.7	41	6	0.6	1	0.10	17.1
55-59	4.1	63	6	0.3	0	0.00	9.5
60-64	4.7	170	32	0.8	5	0.12	21.8
65-69	6.2	166	30	1.0	5	0.16	21.1
70-74	7.8	145	31	1.3	3	0.13	23.4
Total	5.6	585	105	0.8	14	0.11	20.3

HM-JACKarc - Men - subsequent screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	%	CRC N	%	PPV AN N
50-54	3.5	8	4	0.9	0	0.00	50.0
55-59	4.2	34	10	1.1	0	0.00	29.4
60-64	4.4	64	19	1.1	1	0.06	31.3
65-69	5.8	72	15	1.0	2	0.14	23.6
70-74	6.8	57	11	1.0	0	0.00	19.3
Total	5.1	235	59	1.1	3	0.05	26.4

HM-JACKarc - Women - subsequent screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma N	%	CRC N	%	PPV AN N
50-54	2.8	14	1	0.2	0	0.00	7.1
55-59	3.1	28	5	0.5	1	0.09	21.4
60-64	3.4	64	9	0.4	3	0.14	18.8
65-69	3.8	57	4	0.2	4	0.24	14.0
70-74	6.1	53	8	0.7	5	0.42	24.5
Total	3.9	216	27	0.4	13	0.19	18.5

HM-JACKarc - Total- subsequent screening

Age (years)	FIT positive N	Colonoscopy N	Advanced adenoma * N	%	CRC * N	%	PPV AN * N
50-54	3.1	22	5	0.5	0	0.00	22.7
55-59	3.6	62	15	0.8	1	0.05	25.8
60-64	3.8	128	28	0.7	4	0.10	25.0
65-69	4.7	129	19	0.6	6	0.19	19.4
70-74	6.4	110	19	0.8	5	0.22	21.8
Total	4.4	451	86	0.7	16	0.13	22.6

* **p (**OC-Sensor vs HM-JACKarc **)** = NS
PPV=positive predictive value; **AN=**advanced neoplasia – CRC+advanced adenoma