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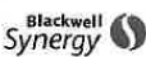
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Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochemical, Fecal Occult Blood Screening Test

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- OBJECTIVES:** Guaiac fecal occult blood colorectal cancer (CRC) screening tests (FOBT) are faulted for low sensitivity and nonspecificity for human hemoglobin (Hb). Automated-developed, immunochemical, human Hb FOBT (I-FOBT) is specific, eliminates diet restrictions, and Hb quantification allows selection of a threshold for colonoscopy. Aims were to determine 1) test reproducibility; 2) test stability; 3) inpatient daily I-FOBT variation; 4) test sensitivity and specificity for neoplasia in 500 symptomatic/high-risk patients undergoing colonoscopy; and 5) to correlate fecal Hb measurements with findings.
- METHODS:** The desktop instrument OC-Sensor (Eiken, Japan) automatically develops and quantitates 50 tests/h for Hb. Patients prepared three tests, which were quantified and then 1) repeatedly re-examined; 2) stored at 4°C or 20°C or 28°C and repeatedly examined; and 3) fecal Hb levels were correlated with colonoscopic findings.
- RESULTS:** Five I-FOBTs re-examined five times in 1 day had no significant measurement changes. Thirty tests stored for 21 or more days had a decay/day of $0.3\% \pm 0.4$ at 4°C (NS), $2.2\% \pm 1.7$ at 20°C (NS), and $3.7\% \pm 1.8$ at 28°C ($p < 0.05$). There were inpatient variations between the three daily I-FOBTs (NS). At the recommended 100 ng Hb/mL threshold, all six cases of CRCs and 20 out of 28 cases of advanced adenomas were detected; evaluated together their sensitivity and specificity were 76.5% and 95.3%.
- CONCLUSIONS:** Desktop, automated-developed, quantitative I-FOBT is now available. Refrigerated OC-Sensor samples are stable for 21 days, easy to prepare and develop and, at the 100 ng Hb/mL threshold, have high sensitivity, specificity, and negative predictive values for significant neoplasia. Suitability for population CRC screening awaits further evaluation.

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The standard guaiac fecal occult blood test (G-FOBT) is faulted for its low sensitivity for significant colorectal neoplasia [colorectal cancer (CRC) and advanced adenomatous polyps (AAP)], and low specificity due to nonspecificity for human hemoglobin (Hb); see reference (1). It is also faulted by the possibility of inaccurate development and evaluation by inadequately trained personnel (2–4).

The introduction of central laboratory and office-developed, immunochemical, fecal occult blood tests (I-FOBT) specific for human Hb improved specificity (5–11). However, for the office-developed tests, the I-FOBT manufacturers have predetermined the degree of sensitivity for Hb, and the occasional experience with more complex office-development was not conducive for large-scale screening and maintaining quality control (1–4, 8, 11).

The automated-developed and quantitative I-FOBT is human Hb specific, eliminates the need for diet restrictions, and the Hb quantification allows selection of a suitable threshold level for follow-up colonoscopy (5–7, 9–12).

The introduction of such methodology, for large-scale screening, requires evaluation of the instrument and its performance characteristics. In addition, we need to evaluate its true sensitivity and specificity for colorectal neoplasia versus colonoscopy in different clinical settings and determine which level of fecal Hb should trigger follow-up colonoscopy.

Specific aims were to determine 1) test-development reproducibility; 2) effect of temperature and duration of storage on fecal sample stability; 3) inpatient daily I-FOBT test variation; 4) sensitivity and specificity for neoplasia found

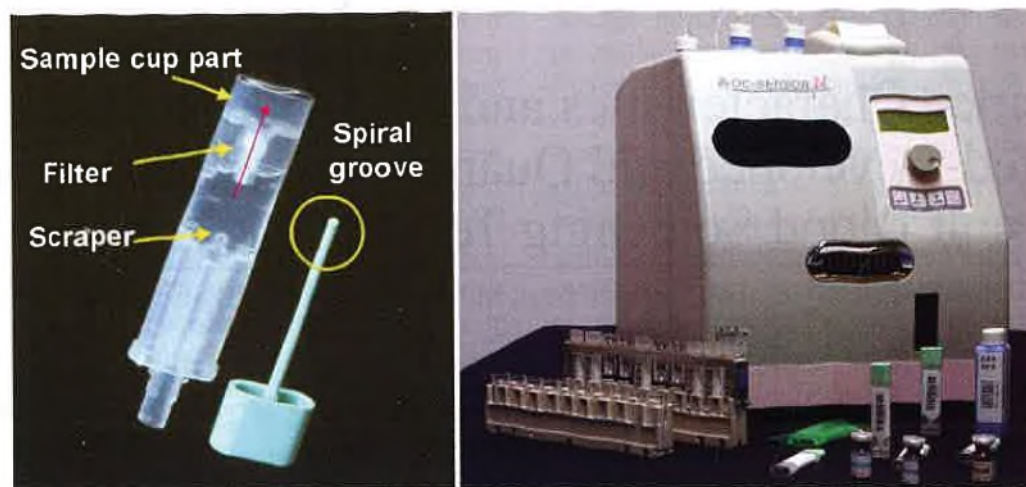


Figure 1. Left: Stool probe and fecal sample storage tube. The closed tube is 8 cm long, 2 cm wide. On each tube there is a unique bar code and space to write name and date. Right: Desktop instrument and accessories. The instrument is 32 cm wide, 53 cm deep, and 42 cm high.

in persons also undergoing colonoscopy; and 5) to correlate fecal Hb levels with clinical findings.

METHODS

Patients

These were ambulatory persons who were symptomatic and scheduled for colonoscopy, or asymptomatic persons at high-risk for CRC and invited for colonoscopy. The latter included surveillance postpolypectomy and those having a family history of colorectal neoplasia. Exclusions included visible rectal bleeding, known diagnosis of inflammatory bowel disease, hematuria, menstruation, and noncooperation with preparing a fecal test.

All participants received an oral and/or telephone explanation of the tests and written instructions on preparing the I-FOBTs.

Colonoscopy was to the cecum or up to an obstructing carcinoma if present. Otherwise, an incomplete examination was repeated or excluded from analysis. All lesions were noted, biopsied, or removed. Patients' electronic data files were available from the three participating endoscopy units belonging to the same medical organization.

Numbers of polyps were noted as were their sites. Pathology reports were available and pathology specimens reviewed when necessary. Polyps were classified as non-adenomas or adenomas. Adenomas were grouped by size: <5 mm, 5–9 mm, ≥ 10 mm; and also by their histology: tubular, tubulo-villous, villous; dysplasia was classified as low-grade dysplasia (LGD) or high-grade dysplasia (HGD). "Significant" neoplasia included CRC or advanced adenomatous polyps (AAP); this latter category included adenomas ≥ 10 mm, or having more than 20% of villous histology or any amount of HGD independent of size. All AAPs <10 mm were re-examined to confirm their histology diagnosis.

Patients with symptoms or having a positive I-FOBT unexplained by their colonoscopy findings continued their investigations. These included upper-gastrointestinal endoscopy and small bowel investigation when appropriate.

The study was approved by the Ethics Committee of the Rabin Medical Center in 2004. All participants gave an informed, signed consent for the I-FOBT and colonoscopy examination.

Fecal Sampling

The fecal test sampling device is shaped like a small test tube with the fecal probe inserted into it and sealing it. The probe has a serrated tip, which is poked into the stool and then pushed back into the tube, past a scraper, and through a membrane into the sample cup. These remove most of the excess feces and leave the stool collected (about 10 mg) into the serrations (Fig. 1). The tip is then put in a closed amount of Hb stabilizing buffer. Each sample tube has a unique bar code and before preparing the sample the patient writes his name and date on the tube. The examinee is requested to prepare three consecutive daily samples during the week before colonoscopy examination. Samples are double-closed in zip-lock bags and kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.

Instrument and Testing and I-FOBT Analysis and Control

The instrument used for developing and quantification of the I-FOBT is OC-Sensor, Eiken, Japan. This is a desktop instrument weighing 26 kg, and is 32 cm wide, 53 cm deep, and 42 cm high. It is self-contained with reagent, buffer, washing and fluid-disposal bottles, and requires access to a standard power supply (Fig. 1). Ten of the patient-prepared fecal sample tubes are loaded into the sample rack, and in parallel there is another rack with disposable reaction cells. The instrument automatically mixes the fecal buffer solution with the latex-antihuman HbA antibody reagent. Following the development cycle, there is automatic flushing of the system.

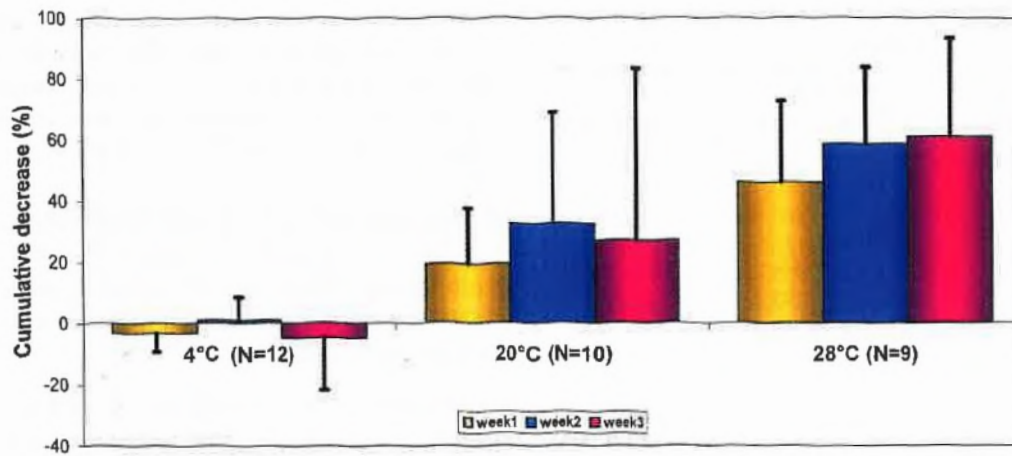


Figure 2. Progressive changes in fecal Hb measurements at end of the first, second, and third weeks' storage at 4°C, 20°C, and 28–30°C. The cumulative changes (decay) at 28°C were significantly different ($p < 0.05$) from the initial measurements.

The flocculation is read as an optical change and compared to a standard calibration curve. Calibration is prepared for each day's analysis, using the provided known high- and low-value control test fluids. The range of measurements is 50–2000 ng Hb/mL, approximately equivalent to 40–400 μg Hb/g feces.

Evaluations Performed

Five I-FOBT samples were each repeatedly re-examined five more times in 1 day. Thirty I-FOBT samples, having >100 μg Hb/mL initial measurements, were stored at 4° or 20° C or at ambient summer room temperature (28–30°C). They were repeatedly re-examined every second day for 3 wk. Further 12 samples, having low but elevated initial Hb levels between 100 and 200 ng/mL, were stored at 4°C and re-examined as above.

Analysis and Statistical Methods

All statistical analyses were performed using the SAS system for Windows, version 8.01. Results are given as mean $\pm$ standard deviation (SD). Stability of the test measurements and effects of duration of storage and temperature were analyzed by analysis of variance with repeated measurements. Weekly changes in the stored I-FOBTs were determined by comparing the lowest value measured in week 1, 2, and 3 with the initial values measured.

For clinical correlation to I-FOBT levels, the most severe pathology finding (histology and polyp size) recorded was used for each examinee.

Persons having only hyperplastic polyps were included in the group not having neoplasia. For analysis of adenomas, the analysis included AAP and was then repeated without them. For the category of "significant" colorectal neoplasia, the analyses included only CRC or AAP or both together.

I-FOBT analysis was based on the 100 ng Hb/mL threshold. These analyses were then repeated at increments of 25 ng Hb/mL down to 50 ng and up to 200 ng Hb/mL for analyses correlating I-FOBT results and presence of neoplasia.

RESULTS

Test Reproducibility

Five prepared I-FOBT samples were quantified and repeatedly examined five more times in 1 day. They had no significant variation in measurements, $F_{(5,20)} = 0.24$, $p = 0.66$.

Test Stability

Thirty I-FOBT samples, positive for Hb and stored at 4°C, 20°C, or 28–30°C, were repeatedly re-examined. Their initial values ranged from 1032 ± 783 to 787 ± 393 ng Hb/mL. The decay/day was $0.3\% \pm 0.4$ at 4°C (NS), $2.2\% \pm 1.7$ at 20°C (NS), and $3.7\% \pm 1.8$ at 28°C ($p < 0.05$). Their cumulative weekly change in I-FOBT measurements is shown in Figure 2. At 4°C, all these I-FOBT samples maintained their elevated fecal Hb levels for 21 or more days.

We repeated the study with a further 12 I-FOBT samples, stored at 4°C, having low but elevated initial measurements ranging from 104 to 233 ng Hb/mL. In two samples, with the lowest initial values, the repeated measurements were <100 ng Hb/mL by 3 wk from the time of preparation by the patient.

Patient and Colonoscopy Results

I-FOBTs were prepared by 521 patients. However 21, having a negative FOBT but incomplete colonoscopy examination, were excluded from this analysis. They confirmed their negative colonic examination by radiology.

The complete data from the initial 500 examinees were analyzed. They include 53.2% males, with a mean age of 62.1 ± 12.6 yr. The symptomatic patients coming for colonoscopy were of average risk in 57.5% while 32.7% had a family history of CRC and 53.4% of the latter were asymptomatic.

Colonoscopy detected non-neoplastic (hyperplastic) polyps in 12.8% and adenomas in 22.4% of the examinees. They included tubular adenomas in 18.8%, tubulo-villous in 3.2%, and villous adenomas in 0.4%. It was observed that 58.8% of the adenomatous polyps were <5 mm, 21.1% were

Table 1. Fecal Occult Blood Levels Detected According to Colonoscopy and Pathology Findings

Diagnosis	No.	Fecal Hb (ng/mL) (Mean $\pm$ SD)	Significance*
Normal†	381	29.1 $\pm$ 103.8	
Adenomas			
All	113	231.9 $\pm$ 567.5	NS
Non-AAP	85	58.0 $\pm$ 156.5	NS
AAP	28	759.8 $\pm$ 935.7	$P < 0.01$
Cancer	6	1154.3 $\pm$ 793.0	$p < 0.01$
CRC + AAP	34	829.4 $\pm$ 913.8	$p < 0.01$

AAP = advanced adenomatous polyps; CRC = colorectal cancer.

* As compared to the normal group.

† Includes 64 patients with only hyperplastic polyps.

6–9 mm, and 20.2% were ≥ 10 mm; 11.4% of the patients had single adenomas, 11.6% had multiple adenomas. LGD was reported in 13.4% examinees, and HGD or cancer in 3.2% of the examinees.

Significant neoplasia was found in 34 patients (6.8%). These included 6 with CRC and 28 with AAP and were significantly more males ($p = 0.01$) and older than 65 yr of age ($p < 0.01$).

Fecal Occult Blood Results

For the entire population undergoing colonoscopy, the mean I-FOBT measurement was 49.0 ± 216.5 ng Hb/mL for sample 1, 41.0 ± 207.1 for sample 2, and 51.3 ± 237.6 for sample 3 ($p = 0.5$). At the Hb threshold of 100 ng Hb/mL, the overall positivity was 9.6%, rising to 15.0% at the 50 ng Hb/mL threshold. Conversely, positivity fell to 7.8% at the 200 ng Hb/mL threshold.

The I-FOBT results according to endoscopy and pathology diagnosis are given in Table 1. The mean I-FOBT values from patients having significant colorectal neoplasia were significantly different from those having a normal colonoscopy examination; $p < 0.01$ (Figures 3 and 4).

Correlations of I-FOBT with Diagnosis

CANCER. Six patients with CRC were identified by colonoscopy. They were identified by utilizing all three I-FOBTs. Five were identified by sample 1, four by sample 2, and all six by sample 3.

ADVANCED ADENOMATOUS POLYPS. Twenty-eight patients were identified by endoscopy and 20 of them by utilizing the measurements of all three I-FOBTs.

SIGNIFICANT NEOPLASIA. These include the six patients of CRC and 28 patients of AAP, and of these 34, 26 were identified by utilizing the measurements of all three I-FOBTs. Eighteen patients were identified by both samples 1 and 2, 21 by sample 3. The sensitivity and specificity results of the I-FOBTs at the standard 100 ng Hb/mL threshold were 76.5% and 95.3%, respectively (Figs. 3 and 4). Similar analyses at lower and higher I-FOBT Hb thresholds and identification by the three I-FOBTs is given in Table 2.

INTRAPATIENT I-FOBT VARIATION. The relative sensitivity of each of the three I-FOBTs for CRC or CRC and AAP, at the 100 ng Hb threshold, and their additive values are given in Table 3. The best results were obtained when all three tests were performed and utilized for analysis.

POLYPS. This refers to the most significant polypoid lesion identified in the screenee. In 175 of the 500 examinees,

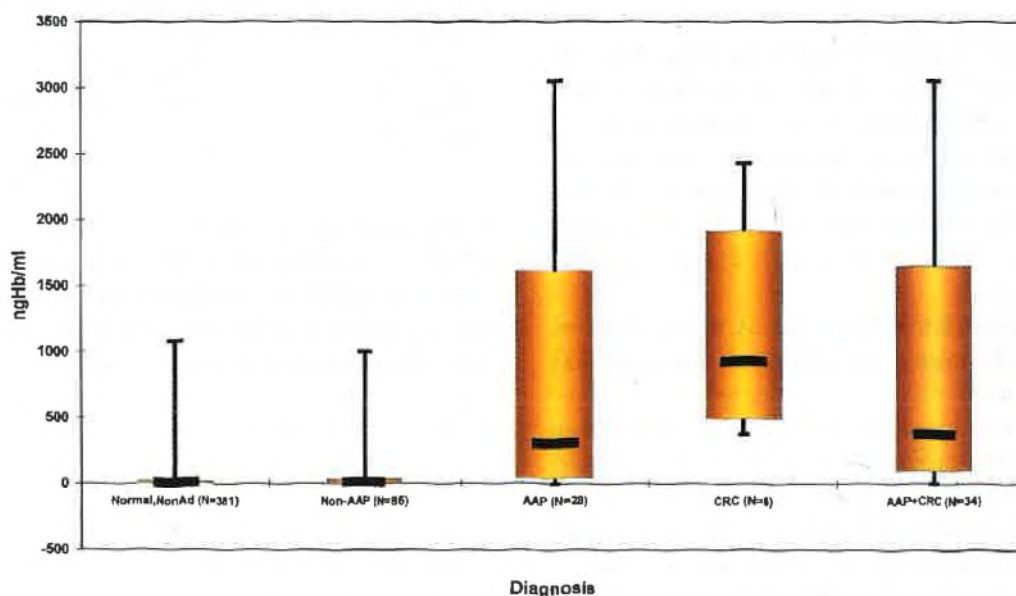


Figure 3. Box plots of fecal Hb values for each diagnostic category. Dark line indicates median Hb value, colored block covers the upper and adjacent two lower quartiles, bars are the maximum and minimum levels measured. CRC and/or AAP measurements are significantly elevated as compared to the normal-hyperplastic polyp group, $p < 0.01$.

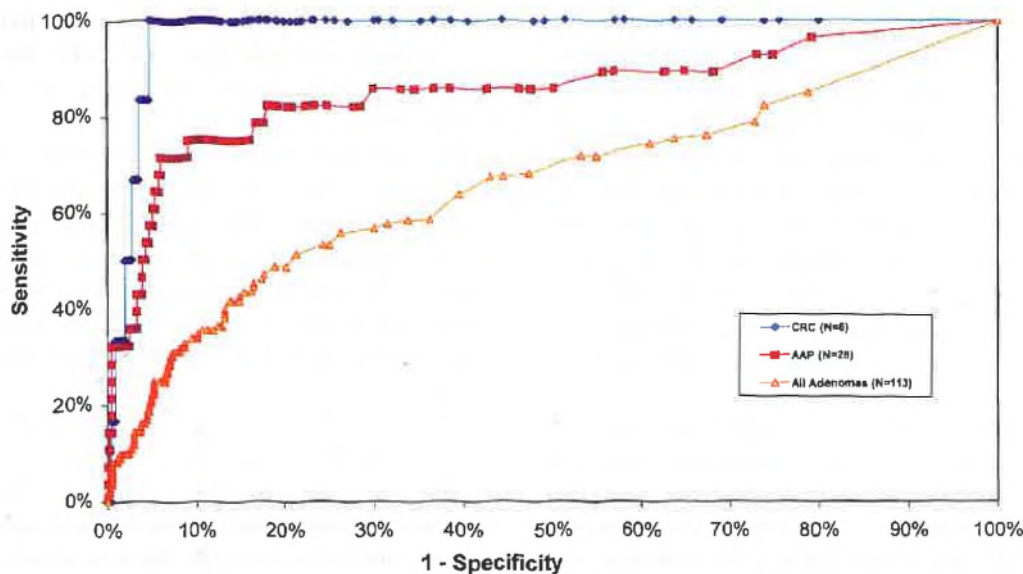


Figure 4. Receiver-operator characteristic curve for sensitivity and specificity for each diagnostic category at the 100 ng Hb/mL threshold for fecal blood measured. There is high sensitivity for CRC and also AAP, with low sensitivity for adenomas as a category.

a polypoid lesion was identified. In 64, the polyp was not an adenoma but a hyperplastic polyp. In 93 screenees, the polyp was a tubular adenoma, whereas 16 had tubulo-villous and 2 had villous adenomas; the remaining 7 had not been recovered for full histological examination.

The sensitivity of the I-FOBT for identifying an adenomatous polyp is shown in Figures 3 and 4. There was a low sensitivity for adenomatous polyps sized <10 mm. Utilizing the results of all three I-FOBTs, at the 100 ng Hb/mL threshold, the sensitivity for adenomas ≥ 10 mm was 82.6%, 6–9 mm was 20.8%, and <5 mm was 9.0%. There was no significant difference in the mean I-FOBT measurements, whether the adenomas were single or multiple ($p = 0.4$).

Screenees with False-Negative or False-Positive I-FOBT Results

This group refers to the eight screenees with AAP who had I-FOBT levels <100 ng Hb/mL. Of the 28 screenees found by colonoscopy to have an AAP, 20 had I-FOBT measurements >100 ng Hb/mL. The values ranged from a low of

107 to a high of 3050 ng Hb/mL (mean 1056 ng). The other eight, with low I-FOBT values, had only a mean of 19 ng Hb/mL.

Conversely, 21 screenees, without significant colorectal neoplasia, had an I-FOBT measurement >100 ng Hb/mL, while the entire normal group had mean measurement of 47.2 ng Hb/mL. These 21 patients are being evaluated and followed up clinically. Five had known iron-deficiency anemia; 10 had adenomas <10 mm in diameter, 1–6 in number. All 21 screenees had had a gastroscopy examination, and in 15 there were significant findings (including multiple findings): esophagitis (2), hiatus hernia (1), gastritis (8), status postgastric surgery (3), gastric carcinoid (1), and duodenitis (4).

DISCUSSION

This colonoscopy-controlled study allowed for a detailed evaluation of an automated desktop instrument for quantitative, immunochemical determination of fecal occult blood. The clinical evaluation demonstrated a high sensitivity of 76.5% for all significant colorectal neoplasia and acceptable specificity of 95.3%.

The technical evaluation included studies of reproducibility of the instrument in developing and evaluating the tests

Table 2. Sensitivity and Specificity for Significant Colorectal Neoplasia, (N = 34)* at Differing Fecal Hb Levels (N = 500)[†]

Fecal Hb (ng/mL)	Sensitivity (%)	Specificity (%)
50	79.4	89.7
75	76.5	93.3
100	76.5	95.3
125	70.6	95.7
150	70.6	95.9
200	64.7	96.3

*Six colorectal cancers and 28 advanced adenomatous polyps.

[†]Utilizing the highest of the three I-FOBT measurement in each patient.

Table 3. Sensitivity for Significant Colorectal Neoplasia (N = 34)* for Each I-FOBT[†] Prepared

I-FOBT Positive	Cancer (%)	Cancer + AAP (%)
Sample 1	83.3	52.9
Sample 2	66.7	52.9
Sample 3	100	61.8
Samples 1 and 2	83.3	64.7
Samples 1, 2, and 3	100	76.5

*Six colorectal cancers (CRC) and 28 advanced adenomatous polyps (AAP).

[†]At the 100 ng Hb/mL threshold.

and stability of the prepared fecal occult blood tests. Because of our high ambient temperature this latter point was carefully evaluated, and we showed that the prepared I-FOBT could be kept up to 3 weeks in refrigeration without significant degradation of the test antigen. As we have seen, for low-elevated levels, the measurement could drop below the 100 ng Hb/mL threshold by 3 weeks even when refrigerated. It is important to emphasize, to the patient and to the medical service, the correct storage and duration of storage. The time period of 2 weeks from preparation is adequate for batch processing of accumulated test samples.

For many years, office-developed I-FOBTs have been available in Japan; because of their high peroxidase-containing diet, these tests were found to be more suitable than G-FOBTs (7, 13). For the same reason this was also found to be true in Hong Kong (10). In a population eating a Western-type diet, the problems with dietary peroxidases can be overcome by dietary restrictions and adaptations to the G-FOBT development protocol (1, 14).

The I-FOBT card, laboratory or office-developed, is commonly used in Japan and has become available in the United States, Israel, Italy, and Australia (1, 3, 8, 9, 11, 15–17). However, even though it is more specific than the G-FOBT, because of its manufacturer's-determined fixed sensitivity we did not find it more sensitive than a cheaper G-FOBT of similar sensitivity (8).

The introduction of the instrument-developed, quantitative, fecal occult blood testing allows the physician to choose the optimal fecal Hb threshold level that triggers a follow-up colonoscopy. To validate this premise, we performed this study in high-risk and symptomatic patients undergoing colonoscopy. From this study, we confirmed that the I-FOBT threshold of 100 ng Hb/mL allowed us to detect all the cancers and the majority of advanced adenomas, giving together a sensitivity of 76.5%. Conversely, it provided an acceptable specificity of 95.3% (1). This means that in this group of high-risk and symptomatic patients, all cases of cancer and most advanced adenomas would be detected and a negative test would provide a very high degree of certainty that there was no clinically significant colorectal neoplasia at this round of screening.

At present, we will continue with collecting three annual fecal tests, as we have confirmed the additive clinical value of repeated occult blood testing in this high-risk population. This is in contrast to the annual 2-day, average-risk population I-FOBT collection, as routinely used in Japan, United States, and Australia and 1-day biennial testing as performed in Italy (11, 12, 16–18).

The decision on the number of fecal samples to be obtained and optimal fecal Hb threshold chosen for screening an average risk population will also involve an evaluation of cost-benefit. This will require a prospective colonoscopy controlled or clinical follow-up study in our own population. In Japan, the number of samples collected and thresh-

old chosen were different from those in Italy, namely 2 annual samples and 150 ng/mL fecal Hb threshold in Japan versus 1 biennial sample and 100 ng/mL threshold in Italy (19, 20, 21).

We will now extend this screening study to include asymptomatic but high-risk persons undergoing surveillance colonoscopy, at set intervals, because of a family history of colorectal cancer or follow-up of past colorectal neoplasia (22). The results might influence future screening and follow-up policy and obviously reduce costs, patient inconvenience, as well as demands on medical priorities and services.

The goal will be to extend this automated-developed, quantitative, I-FOBT to colorectal neoplasia screening in the asymptomatic average-risk population. This has been done with the InSure (Enterix, United States, and Australia) test in pilot studies in Australia and also in the United States (9, 11). Another automated test is Magstream (Fujirebio, Japan) developed in Japan and also being evaluated in Australia, France, and Hong Kong (23). Outside Japan, the automated version of OC-Sensor is being used in a large-population, biennial, single sample study in Northern Italy (18, 19). It has been used in a population study in Uruguay (Dr. E. Fenocchi, personal communication). It will also be used in a large Spanish asymptomatic population screening trial (Dr. E. Carballo, personal communication).

The participation rate of preparing a fecal test is critical for the success of a FOBT screening program. To facilitate average-risk compliance, there are two issues that are needed to be addressed. The provision of a toilet-disposable paper stool-collecting device facilitates preparing the test (3). The storage of the prepared I-FOBT in a refrigerator, until development, is important for maintaining the test stability. This is critical in countries with high ambient temperatures, even when homes are air-conditioned. The double zip-lock bags we provided answered some of the screeners' hesitancy about keeping the prepared test transiently in their home refrigerator. This packaging could be further improved.

In conclusion, we have found this desktop, automated-developed and quantified Hb version of the immunochemical fecal occult blood test to provide a highly sensitive test for detecting significant colorectal neoplasia with an acceptable specificity and consequent high negative predictive value. Our forthcoming studies will be focused on asymptomatic high-risk persons and evaluating its suitability as a means for average-risk population screening.

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