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HEALTH TECHNOLOGY ASSESSMENT REPORT

MINISTRY OF HEALTH MALAYSIA

IMMUNOCHEMICAL FAECAL OCCULT BLOOD TEST (IFOBT) FOR COLORECTAL CANCER (CRC) SCREENING

MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

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DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organisations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

Please contact : www.htamalaysia@moh.gov.my, if you like further information.

For further information please contact:
Health Technology Assessment Section (MaHTAS),
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya
Tel: 603 88831246
Fax: 603 8883 1230

Available at the following website:
http://www.moh.gov.my,

AUTHORS

Mr. Syful Azlie bin Md Fuzi
Senior Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Junainah binti Sabirin
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Prof. Dr. Samsinah binti Hussain
Lecturer
Pharmacy Department
Faculty of Medicine
University of Malaya

EXPERT COMMITTEE

Dato' Dr. Muhammad Radzi bin Abu Hassan
Consultant Physician and Gastroenterologist
Hospital Sultanah Bahiyah, Alor Setar, Kedah

Prof. Dato' Dr. Aminuddin bin Ahmad
Senior Consultant Physician and Gastroenterologist
Universiti Teknologi Mara (UiTM), Shah Alam, Selangor

Dato' Dr. Hj. Rosemi bin Salleh
Consultant Gastroenterologist
Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

Datin Dr. Nik Raihan binti Nik Mustapha
Consultant Histopathologist
Hospital Sultanah Bahiyah, Alor Setar, Kedah

Dr. Jasiah binti Zakaria
Colorectal Surgeon
Hospital Tunku Jaafar, Seremban, Negeri Sembilan

Dr. Hjh. Rosaida binti Mohd Said
Consultant Physician and Gastroenterologist
Hospital Ampang, Selangor

Dr. Tengku Norita binti Tengku Yazid
Consultant Chemical Pathologist
Hospital Selayang, Selangor

Dr. Muhammad Azrif bin Ahmad Anuar
Oncologist and Lecturer
UKM Medical Centre
The National University of Malaysia

EXPERT COMMITTEE (CONT.)

Dr. Nor Saleha binti Ibrahim Tamin
Senior Principal Assistant Director
Disease Control Division
Ministry of Health Malaysia

Datin Dr. Rugayah binti Bakri
Head, Health Technology Assessment Section (MaHTAS),
Deputy Director
Medical Development Division
Ministry of Health Malaysia

EXTERNAL REVIEWERS

Dr. Sia Koon Ket
Consultant Gastroenterologist
Hospital Ampang, Selangor

Dr. Gerard Lim Chin Chye
Senior Consultant Clinical Oncologist & Head of Department
Department of Radiotherapy and Oncology
Hospital Kuala Lumpur
(Head, Radiotherapy and Oncology Service, Ministry of Health Malaysia)

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EXECUTIVE SUMMARY

Background

Colorectal cancer (CRC) is one of the most common forms of gastrointestinal (GI) cancer in the world today. It is the fourth most common form of cancer worldwide and the most frequent in North America, Australia, New Zealand, Argentina, and parts of Europe. According to the latest report of the National Cancer Registry (NCR) in Peninsular Malaysia 2006, CRC was the second most common cancer after breast cancer. It is the first among male and also second among female. The incidence of CRC has increased over the past decade. The age-standardised incidence rate (ASR) was estimated to be 8.1 per 100,000 population in 1987; 11.9 in 1998; and 13.9 in 2002; whereas it was 18.4 in 2006 in Peninsular Malaysia. Although high incidence of CRC was reported, there is no national CRC screening programme implemented. The diagnosis of CRC raises many questions and there is a need for clear, understandable answer, and the only contentious issue is which screening test to use. Therefore, the purpose of this Health Technology Assessment (HTA) on immunochemical faecal occult blood test (IFOBT) was to evaluate whether, and under what conditions, it would be effective, safe, and cost-effective tests for CRC screening among general population in Malaysia.

Technical features

Faecal occult blood refers to blood in the faeces that is not visibly apparent. A faecal occult blood test (FOBT) is designed to identify hidden or small quantities of blood in faecal sample. There are two main types of FOBTs: guaiac-based faecal occult blood test (gFOBT) and IFOBT which is also known as faecal immunochemical test (FIT). Guaiac-based test are the long established and most commonly used in the average risk population for CRC screening programme. However, a wide variety of newer commercially IFOBT are now available, either qualitative or quantitative test methods. The qualitative test method for IFOBT require minimal processing and involve developing a test strip with controls and reading a colour reaction while the quantitative method require more extensive laboratory processing which provide automated instrumental test development and reading with adjustable sensitivity threshold. The reference or gold standard for these tests is colonoscopy with biopsy.

Policy Question

i. Should IFOBT be used in Malaysia as a screening test for CRC?
ii. Which test method (qualitative or quantitative) for IFOBT is the most suitable to be used for CRC screening?

Objective

i. To assess the diagnostic accuracy of the various types of IFOBTs used for CRC screening among general population.

ii. To assess the effectiveness of CRC screening using various types of IFOBT among general population compared to no screening.

iii. To assess the safety of the various types of IFOBT used as a screening test for CRC.

iv. To assess the economic implication of the various types IFOBTs used for CRC screening among general population.
v. To assess whether CRC screening using various types of IFOBT have issues related to the ethical, legal, and organizational aspects.

Methods

Electronic databases such as MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning database, INAHTA database, HTA database and FDA database were searched. No limits were applied to the search. Additional articles were identified from bibliographies of retrieved articles and hand-searching of journals. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) and evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force and NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4(2nd Edition), March 2001 for test accuracy studies.

Results and conclusion:

Diagnostic accuracy and effectiveness

There was fair level of evidence to suggest that the sensitivity and specificity of IFOBT varies with the cut-off points or positivity threshold of haemoglobin. The sensitivity of IFOBT (cut-off point between 100 ng/ml to 150 ng/ml) is around 89.0% for CRC whereas specificity around 97.0%. Positive predictive value (PPV) ranged from 4.0% to 34.0% for CRC and from 11.2% to 40.3% for high risk adenomas. False positive rate ranged from 1.5% to 6.0% for CRC. Immunochemical faecal occult blood test (IFOBT) identified small adenomas (≤ 9 mm) with a level of sensitivity that was higher than the false positive rate (7.0% versus 4.5%, $p<0.001$).

Several studies have revealed that the diagnostic accuracy or performance of IFOBT was influenced by two important factors: high temperature and lag time before the faecal sample is analyzed because of haemoglobin stability. There was a significant difference in the proportion of IFOBT positive results in the summer than in winter as there was a significant fall in haemoglobin concentration at higher ambient temperatures. A recent study has reported that the performance of the IFOBT decreased (occurrence of false negative results) when there was a delay in time between faecal sampling and arrival of the specimen to the laboratory because of haemoglobin degradation.

A two-day faecal collection method was found to be more cost-effective compared to three-day faecal collection method for use in IFOBT as a means of screening for CRC.

A screening programme using IFOBT can be effective for prevention of advanced CRC (risk of developing advanced CRC was reduced from 28.0% to 46.0%) and reduced mortality from 23.0% to 60.0%. Regular IFOBT can detect precancerous lesions and CRC in early stages and thus reduce mortality from CRC.

Safety

There was no retrievable evidence on the safety of IFOBT for CRC screening. However, several test methods on IFOBT have United States Food & Drug Administration (US FDA) approval.

Economic evaluation

There was evidence to suggest that IFOBT or FIT was cost-effective in comparison with no screening. The generated incremental cost-effectiveness ratios (ICERs) were USD$905 and CAN$611 per quality-adjusted life year in Taiwan and Canada, respectively. An economic evaluation in Canada also revealed that annual FIT with mid-range testing characteristics, was more effective and less costly compared to all strategies (including no screening). By using this modality, it was postulated that the number of CRC could be reduced to about 71.0% and the numbers of CRC deaths to about 74.0%, while saving CAN$68 per person.

There was no retrievable evidence on the exact price or cost of the IFOBT fully automated analyzer. However, a population screening programme conducted in Italy (2004) reported that they spent €2,066 for three months on renting the analyzer. In the Malaysian context, the cost for qualitative IFOBT ranged from [redacted] to [redacted] per test.

Recommendation

Based on the above review, IFOBT can be used in Malaysia as a screening test for CRC. The use of fully automated IFOBT assay would be highly desirable should a screening programme is to be introduced because of the large number of tests to be done and involving large number of laboratories. Automation allows time to be saved and could reduce the number of staff required to perform analysis, better standardization of results, and the application of very strict quality control criteria. However, one has to take cognizance of the staff with the skills required to use the automated equipment that they must be well trained.

From the viewpoint of diagnostic validity and cost-effectiveness, the recommended cut-off points varied from 100 ng/ml to 150 ng/ml. A two-day faecal collection method was found to be more cost-effective compared to three-day faecal collection method for use in IFOBT as a means of screening for CRC.

However, organizational issues such as training, manpower, good referral centre or system, and funding as well as sample collection, storage condition, sample analysis, and transportation need to be addressed at all levels. One must recognized methods to minimise the effect of high temperature and lag time before the faecal sample can be analyzed.

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GLOSSARY AND LIST OF ABBREVIATIONS

HTA	Health Technology Assessment
IFOBT	Immunochemical faecal occult blood test
CRC	Colorectal cancer
GI	Gastrointestinal
NCR	National Cancer Registry
ASR	Age-standardised incidence rate
USPSTF	United States Preventive Services Task Force
DCBE	Double-contrast barium enema
CTC	Computed tomographic colonography
DRE	Digital rectal examination
gFOBT	guaiac faecal occult blood test
FIT	Faecal immunochemical test
DNA	Deoxyribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
FOBT	Faecal occult blood test
RPHA	Reversed passive haemagglutination test
LAT	Latex agglutination test
ELISA	Enzyme-linked immunosorbent assay
nm	nanometre
ng/ml	nano gram per millilitre
SU	Standard Unit
mm	millimetre
US FDA	United States Food & Drug Administration
RCT	Randomised controlled trial
CASP	Critical Appraisal Skills Programme
WHO	World Health Organization
PPV	Positive predictive value
NPV	Negative predictive value
HRA	High risk adenoma
GP	General Practioner
ROC	Receiver operating characteristics
OR	Odd ratio
CI	Confident interval
TNM	Tumour Nodes Metastasis
IC	Interval cancer
HRD	Hospital discharge record
AAT	Average ambient temperature
ICER	Incremental cost-effectiveness ratio
PCR	Polymerase chain reaction
L-DNA	Long-fragment DNA
fDNA	Faecal DNA
DIA	DNA integrated assay
QdHPLC	Quantitative-denaturing high performance liquid chromatography
AVG-DIA	Average DIA

HEALTH TECHNOLOGY ASSESSMENT (HTA) IMMUNOCHEMICAL FAECAL OCCULT BLOOD TEST (IFOBT) FOR COLORECTAL CANCER (CRC) SCREENING

1.0 BACKGROUND

Colorectal cancer (CRC) is one of the most common forms of gastrointestinal (GI) cancer in the world today. It is the fourth most common form of cancer worldwide and the most frequent in North America, Australia, New Zealand, Argentina, and parts of Europe.[1] In the United States, it is the third most common cancer diagnosed in both men and women; and for 2010, the estimated number of new cases of colon cancer and rectal cancer were 102,900 and 39,670, respectively.[2] The incidence of CRC has increased over the past decade. The age-standardised incidence rate (ASR) was estimated to be 8.1 per 100,000 population in 1987; 11.9 in 1998; and 13.9 in 2002; whereas it was 18.4 in 2006 in Peninsular Malaysia. According to the latest report of the National Cancer Registry (NCR) in Peninsular Malaysia 2006, CRC was the second most common cancer after breast cancer. It is the first among male and also second among female. A total of 2,866 cases were registered with NCR in 2006 and it represented 13.2% of all cases registered. The incidence was slightly higher among males (ASR of 21.6 per 100,000) compared to females (ASR of 15.4 per 100,000). The incidence was highest among Chinese where the ASR was 21.4 per 100,000 and were lower in Indian and Malay where the ASR was 11.3 per 100,000 and 9.5 per 100,000 respectively.[3]

Colorectal cancer (CRC) is cancer of the colon and the rectum. The colon and rectum are parts of the digestive system, which is also called the gastrointestinal (GI) system (Figure 1). The first part of the digestive system processes food for energy while the last part (the colon and rectum) absorbs fluid to form solid waste (faecal matter or stool) that passes from the body. The colon has four sections: ascending colon, transverse colon, descending colon, and sigmoid colon (Figure 2).[2]

Tumours of the colon and rectum are growths arising from the inner wall of the large intestine. Benign (non-cancerous) tumours of the large intestine are called polyps. Malignant tumours of the large intestine are called cancers. Benign polyps do not invade nearby tissue or spread to other parts of the body. Benign polyps can be easily removed during colonoscopy and are not life-threatening. If benign polyps are not removed from the large intestine, they can become malignant over time.

Most of the cancers of the large intestine are believed to have developed from polyps. Cancer of the colon and rectum (also referred to as CRC) can invade and damage adjacent tissues and organs. Cancer cells can also break away and spread to other parts of the body (such as liver and lung) where new tumours form. The spread of colon cancer to distant organs is called metastasis of the colon cancer. Once metastasis has occurred in CRC, a complete cure of the cancer is unlikely.[2]

In general the population at risk for colorectal cancer can be subdivided into high, average and low risk groups. The following is a summary of this groups.[2]

High risk (≥ 50 years)	• Personal history of either polyps or colorectal cancer. • Family history of either polyps or colorectal cancer. • Personal history of inflammatory bowel disease. • Family history of cancer such as breast, uterine and ovarian.
Average risk	• Asymptomatic individual aged over 40 years.
Low risk	• Asymptomatic individuals aged less than 40 years and other than those listed above.

Figure 1: Gastrointestinal system

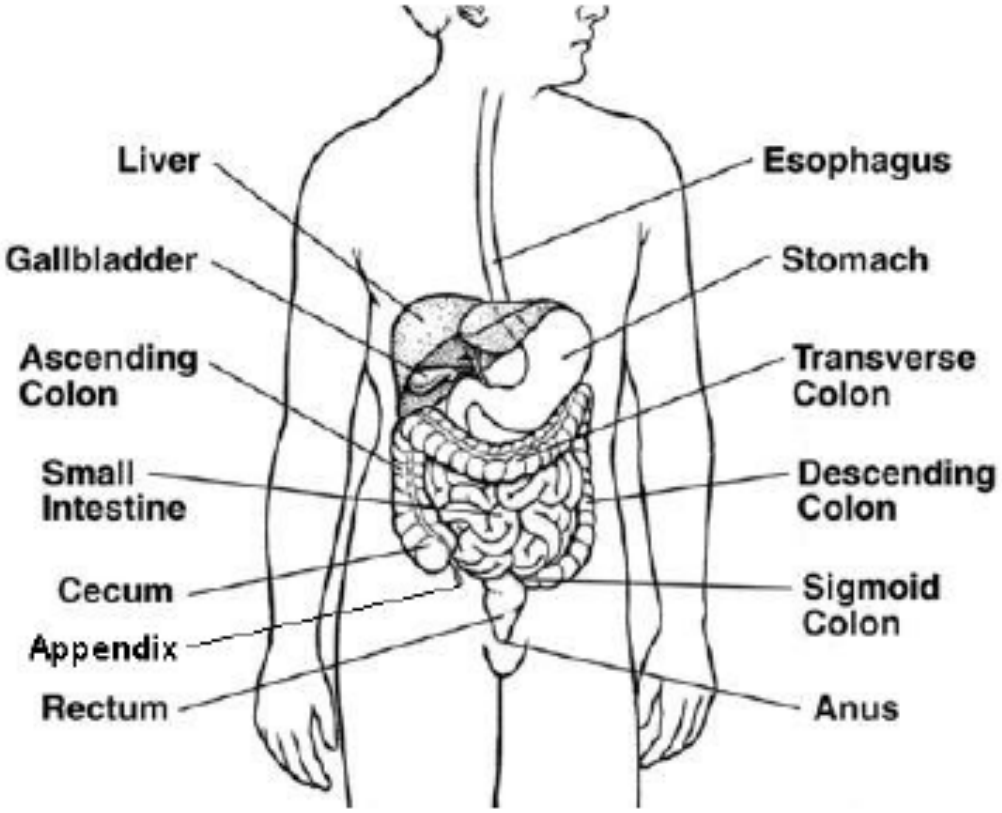
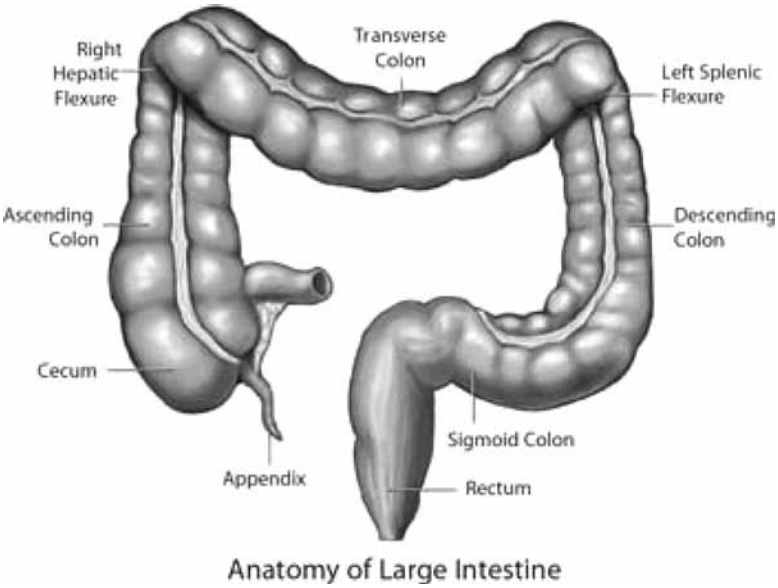


Figure 2: Anatomy of large intestinal (colon)



Several major organizations, including the United States Preventive Services Task Force (USPSTF) which is a group of experts convened by the U.S. Public Health Service, the American Cancer Society, and professional societies, have developed guidelines for CRC screening. Although some details of their recommendations vary regarding which screening tests to use and how often to be screened, all of these organizations support screening for CRC. It is important that a screening test, which is directed at healthy people, have an impact measurable at the population level. People are inherently reluctant to undergo invasive and inconvenient tests for screening such as colonoscopy without strong motivation.[4, 5]

The diagnosis of CRC raises many questions and there is a need for clear, understandable answer. There was evidence to show screening for CRC using gFOBT will reduce CRC mortality [6-8] and the only contentious issue is which screening test to use. The most widely used screening strategy in the average risk population remains the gFOBT whose efficacy was shown in three randomised controlled trials (RCTs).[6-8] However, gFOBT which detects the peroxidise activity of haem or haemoglobin, has important limitations. It is not specific for human haemoglobin and false positive and false negative results can result from certain compounds or medications in food such as red meat, certain uncooked vegetables, vitamin C, and nonsteroidal anti-inflammatory drugs (NSAIDs); that should be avoided before and during the faecal sample collection period. Another important limitation is the low diagnostic performance for precursors to CRC. As a consequence, alternatives to gFOBT are increasingly becoming a subject of interest. In particular, the IFOBT is often considered as a potential substitute for gFOBT. Immunochemical faecal occult blood test (IFOBT) that use specific antibodies against human blood components overcome the problem of diet or medication restriction.[9]

In Malaysia, a screening programme for CRC has not been implemented even though high incidence of CRC was reported. At present, surgical resection continues to be the best hope of cure for patients with colorectal cancer. However, by the time the patient presents to the physician with symptoms, the cancer is frequently advanced with little hope of cure. Therefore, a Health Technology Assessment (HTA) is required to look into the suitability of using IFOBT for CRC screening in general population. This HTA was requested by the Consultant Physician and Gastroenterologist in Hospital Sultanah Bahiyah Alor Setar, Kedah.

2.0 TECHNICAL FEATURES

2.1 Colorectal cancer (CRC) screening test

There are several different tests that can be used to screen for CRC. The test can be divided into two broad groups: [2]

i. Tests that can find both colorectal polyps and cancer

These test will look at the structure of the colon itself to find any abnormal areas. This is done either with a scope inserted into the rectum or with special imaging (x-ray) tests. Polyps found before they become cancerous can be removed, so these tests may prevent CRC. This includes flexible sigmoidoscopy, colonoscopy, double-contrast barium enema (DCBE), CT colonography (virtual colonoscopy), and digital rectal examination (DRE). However, these tests are invasive and may not be acceptable as a primary screening tool in asymptomatic individuals.

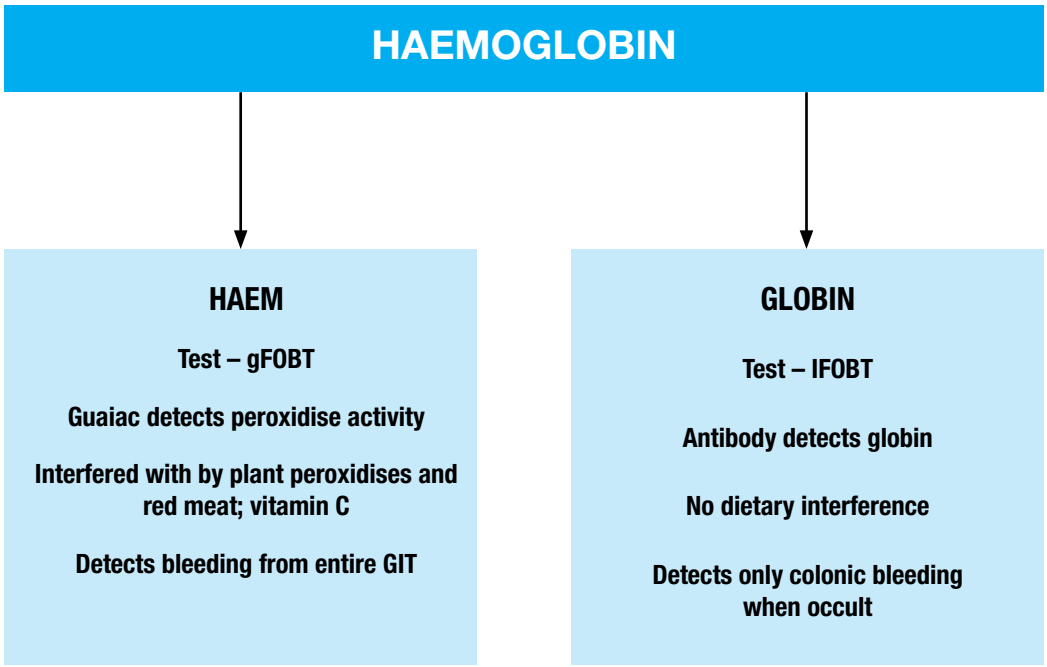
ii. Tests that mainly find cancer

These involve testing the stool (faeces) for sign of occult or hidden blood that may be present. These tests are less invasive and easier to be conducted such as guaiac-based faecal occult blood test (gFOBT), immunochemical faecal occult blood test (IFOBT) which is also known as faecal immunochemical test (FIT), and faecal DNA test. The rational of using this technology as a screening test is based on the concept that blood vessels at the surface of larger colorectal polyps or cancers are often fragile and easily damaged by the passage of faeces and will bleed, and therefore become detectable.

2.2 Faecal occult blood test (FOBT): Technology description

There are two types of commercially available FOBTs: the long established gFOBT and the newer IFOBT. The gFOBT detects haem while the IFOBT detect globin (Figure 3).[5]

Figure 3: Scheme for haemoglobin breakdown in faeces and associated issues with the two FOBT technologies



Detection of haem by gFOBT is dependent on the peroxidise activity of haem. Dietary peroxidises (found in a range of certain fruit and vegetables especially if raw) can cause false positive results with gFOBT. Dietary haem from red meat also causes false positive results. Antioxidants such as vitamin C may interfere with the chemistry of the reaction to cause false negative results. Haem is also reasonably stable in the gut and gFOBT may detect bleeding from any site in the GI tract although they are more sensitive for lower GI bleeding. This means that gFOBT are not selective for bleeding from colon or rectum.[5]

Detection of globin by IFOBT is based on antibodies which are generally specific for human haemoglobin and some of its luminal-derived degradation products. IFOBT are not subject to interference by diet or drugs and do not require proscription of any foods or drugs prior to sampling faeces. As globin is rapidly digested in stomach and small intestine, IFOBT are much more selective for occult bleeding of colorectal origin than gFOBT.[5]

In general, FOBT involve sample preparation prior to colorimetric visualisation.

This may be conducted in the home, clinician's office or a pathology laboratory. The most accepted regimen for faecal occult blood testing involves two faecal samples for three consecutive days. There are several alternative sampling methods associated with faecal occult blood testing. These include utilising either a wooden spatula or a brush, method which involve a different degree of stool handling. The samples are then usually transferred onto a sample card which can be delivered by post to the appropriate location for development and interpretation. A single positive sample in the series is counted as a positive result. Nearly all FOBT manufacturers make analytical sensitivity claims (in vitro detection limits). The analytical sensitivity of a test represents the smallest amount of substance that can be measured in a biological sample. Examples of these sensitivity claims from manufacturer's product sheets are listed below (Table 1).[10, 11]

Table 1: In vitro detection limits of commercially available FOBTs

Product	Type	Manufacturer	In vitro detection limits
Hemoccult®	guaiac	Beckman Coulter Inc.	50% at 300 µg Hb/g faeces
Hemoccult® II			
Hemoccult® SENSA®	guaiac		75% at 300 µg Hb/g faeces
Hemoccult® II SENSA®			
Hemoccult® ICT	immuno		30 µg human Hb/g faeces
FlexSure® OBT	immuno		300 µg human Hb/g faeces
Magstream HemSp®	immuno		300 µg human Hb/g faeces
Instant-View® FOBT II	immuno	Alpha Scientific Desings Inc.	50 µg human Hb/g faeces
InSure®	immuno	Enterix, Inc.	50 µg human Hb/g faeces
ImmoCARE®	immuno	Care Products, Inc.	30 µg human Hb/g faeces
ColonCARE®			
HemeSelect®	immuno	Fujirebio (Japan)	300 µg human Hb/g faeces
Immudia HemSp®			
OC-Hemodia®	immuno	Eiken Chemical (Japan)	40 µg human Hb/g faeces
MonoHaem®	immuno	Nihon Pharmaceuticals (Japan) Chemicon International, Inc. (Australia)	1 to 2 mg Hb/g faeces
Sure Vue®	guaiac	Fisher Scientific Co. Inc.	0.3 mg Hb/g faeces
Coloscreen® ES	guaiac	Helena Laboratories Inc.	0.3 mg Hb/g faeces
Sure Vue® ES	guaiac	Fisher Scientific Co. Inc	2 mg Hb/g faeces
HemaPrompt®	guaiac	Aerscher Diagnostics Inc.	10 mg Hb/g faeces
Hemostick®	immuno	Ventec S.A. (Belgium)	100 µg human Hb/g faeces
Actim Fecal Blood®	immuno	Medix Biochemica	25 to 50 µg human Hb/g faeces

2.3 IFOBT: Methods and brand names

Aside from the classical gFOBT, there has been the development of IFOBT specifically designed to detect human haemoglobin in dried faecal samples. They involved the use of an anti-human monoclonal antibody, targeted at intact human blood-borne proteins (usually haemoglobin). These tests therefore have the theoretical advantage of not being affected by haem, peroxidases or anti-oxidases in the diet. In addition, immunochemical tests will not detect proximal bleeds, since in this case haemoglobin is digested before being passed in the faeces.[10]

A wide variety of newer commercially IFOBT are now available, either qualitative or quantitative methods such as reversed passive haemagglutination tests (RPHA), latex agglutination tests (LAT), the enzyme-linked immunosorbent assay (ELISA), the fluorescence enzyme immunoassay, the gold-coloric method and the immunocolorific method. The qualitative test method for IFOBT require minimal processing and involve developing a test strip with controls and reading a colour reaction while the quantitative method require more extensive laboratory processing which provide automated instrumental test development and reading with adjustable sensitivity threshold.[11]

Some of the IFOBT brand names that have been widely used as a screening test for CRC screening programmes (Japan, China, Taiwan, Italy, Germany, Netherlands, Canada and Uruguay) were **Immudia Hem-Sp or Hemeselect** (qualitative; RPHA), **Monohaem** (qualitative; immunocolorific method), **OC-Hemodia** (qualitative; latex agglutination test) developed with the **OC-Sensor Micro** (quantitative, fully automated instrument; latex agglutination test), **FOBT Gold** (quantitative, fully automated instrument; latex agglutination test), and **Magstream 1000/Hem SP** (quantitative, fully automated instrument; magnetic particles agglutination).[16-30]

2.3.1 Immudia Hem-Sp (Fujirebio, Tokyo, Japan) or Hemeselect (SmithKline Diagnostic, Palo Alto, California, USA)

These RPHA tests used chicken-erythrocytes coated with antibodies to human haemoglobin. The coated chicken-erythrocytes are agglutinated in the presence of haemoglobin in human faecal sample. Immudia Hem-Sp or Hemeselect were interpreted at 1:8 dilutions according to two positivity thresholds: positive (+) or borderline (±). After erythrocytes coated with anti-human haemoglobin antibodies were added to the diluted extract of faecal specimens, test reactions were consider negative when no agglutination was evident. Reactions were considered as borderline (±) when erythrocytes formed a ring around a compact button, slightly greater in diameter than in control well, with slight peripheral agglutination. Immudia Hem-Sp or Hemeselect was considered positive (+) when erythrocytes formed a ring greater in diameter and thinner than that in the negative control well or appeared filmy and spread out, uniformly covering the well bottom with or without centripetal sliding.[16, 27, 29]

2.3.2 Monohaem (Nihon Pharmaceutical, Japan)

The Monohaem test incorporates an immobilised monoclonal antibody on a slide which selectively binds human haemoglobin from the faecal sample. The principles and procedures of the immunological slide Monohaem are as follows: firstly, those being screened are asked to make a thin faecal smear on the test filter paper. If human haemoglobin is present in the faecal sample, an antigen-antibody reaction will occur with the monoclonal antibody in the filter paper. The reacted sample is then washed to remove components other than the haemoglobin and a colour coupler is added. Oxygen is dissociated from hydrogen peroxide by the peroxidise-like activity of the human haemoglobin, which oxidises tetramethylbenzidine, leading to the subsequent appearance of a green colour. The presence of human haemoglobin is thus indicated by the appearance of this green coloration. The procedures of this test are uncomplicated.[24]

2.3.3 OC-Hemodia and OC-Sensor Micro (Eiken, Tokyo, Japan)

OC-Hemodia is an IFOBT based on the reaction of latex agglutination by antibody specific to human haemoglobin, and developed with the 10-tube rack OC-Sensor Micro, a fully automated analyzer allowed an average processing of approximately 100 tests per hour. The principles and procedures of the immunological slide, OC-Hemodia are as follows: the instructions provided with the kit required sampling stools at six different points, placing the stool samples in a test tube filled with a buffer solution (ammonium) and returning the samples to the centre in a cold box. For the processing of the tests, the OC-Sensor Micro was used with quantitative determination. Two drops from the liquid containing the faecal samples in the test tube are put in round wells and mixed with an anti-human haemoglobin antibody that is attached to polystyrene latex particles. The assay is based on the flocculation reaction between the agglutinated human haemoglobin/polystyrene latex complexes and measured by reading flocculation as an optical change (increased absorbance at 660 nm) compared to a standard calibration curve. This automated immunochemical system measures agglutination optically with a haemoglobin concentration range 0 to 1,200 ng/ml. The detection threshold (cut-off) can be adjusted by the user to the concentration determined by screening programme. The procedures of this commercial test are not complicated and are performed in a hospital laboratory or a physician's office.[16-18, 20-22, 25-26, 28, 30]

2.3.4 FOBT Gold (Sentinel Diagnostics, Milan, Italy)

FOB Gold is a fully automated assay developed with the Aeroset instrument (Abbott Diagnostics, Abbott Park, USA), a quantitative latex antigen-antibody agglutination assay that uses polyclonal anti-human haemoglobin antibodies that can also be run on high throughput automated clinical chemistry analysers, allowed an average processing of approximately 500 tests per hour. The assay is based on the flocculation reaction between human haemoglobin and polyclonal anti-haemoglobin polystyrene-adsorbed antibody. The haemoglobin concentration is measured by reading flocculation as an optical change (increased absorbance at 572 nm and 804 nm) compared to a standard calibration curve. The cut-off points is set by the user.[22, 30]

2.3.5 Magstream 1000/Hem SP (Fujirebio, Tokyo, Japan)

Magstream 1000/Hem SP is based on the Immudia Hem-Sp test, which was the original version of Hemeselect (Beckman Coulter, Palo Alto, California, USA). The haemagglutination technique using chicken red cells in the Immudia Hem-Sp test was replaced by magnetic particles agglutination. The system used an immunologic indirect agglutination method to detect faecal occult blood with rabbit anti-human haemoglobin, which was attached to magnetic gelatine particles. This modification led to faster agglutination and produced a more stable agglutinate, which allowed automated result interpretation. Agglutination of the magnetic gelatine particles was accelerated by the use of magnetic force to draw particles together at the bottom of a V-shaped well. The plate then was titled to 60° from horizontal to allow free magnetic particles to run down the slope of the well and form a measurable line. In the presence of human haemoglobin, particles remained in the shape of a tight button or a short line during tilting. The length of the line was determined optically using reflected 690 nm light and was measured in standard units (SU) (1 SU=0.03 mm). The cut-off recommended by the manufacturer was 100 SU, but the cut-off level was adjustable.[23]

2.4 Competing technology: faecal DNA testing

Faecal sample testing using molecular diagnostic tests is emerging as a potentially important new approach that has the potential of providing accurate and cost-effective, early detection of CRC. The most prominent of genetically based faecal tests exploits the concept of chromosomal instability with mutations progressively accumulating in the adenomatous polyposis coli, p53 tumour suppressor genes, and the K-ras oncogene.

This test relies upon preservation of naked DNA in human stool samples. The test requires a large-volume faecal sample from which purified DNA is prepared using oligonucleotide-based hybrid capture. The genetic mutation sites are detected and quantified with real time polymerase chain reaction (PCR). A different marker found in DNA from cancer cells exfoliated into the gut lumen is so-called long-fragment DNA (L-DNA), thought to reflect disrupted apoptosis (normal mode of cell death) in cancer cells.[12]

2.5 Reference or 'Gold Standard'

Clinical sensitivity and specificity are often used to compare the diagnostic capabilities of a test and they traditionally rely on the performance of a given test, used at a specific test threshold, when compared to a reference or 'gold standard' that is supposed to give the 'true' diagnosis. It is mandatory that any positive IFOBT be investigated by an appropriate diagnostic procedure. The 'gold standard' diagnostic procedure and the procedure of choice for this investigation is colonoscopy with biopsy. If the colonoscopy is 'incomplete', then a DCBE is generally used to ensure complete visualisation of the colon. A DCBE plus flexible sigmoidoscopy may replace the colonoscopy if there are difficulties with local availability or expertise, or if the patient prefers.[10, 11]

3.0 POLICY QUESTION

3.1 Should IFOBT be used in Malaysia as a screening test for CRC?

3.2 Which test method (qualitative or quantitative) for IFOBT is the most suitable to be used for CRC?

4.0 OBJECTIVE

4.1 To assess the diagnostic accuracy of the various types of IFOBTs used for CRC screening among general population.

4.2 To assess the effectiveness of CRC screening using various types of IFOBT among general population compared to no screening.

4.3 To assess the safety of the various types of IFOBT used as a screening test for CRC.

4.4 To assess the economic implication of the various types IFOBTs used for CRC screening among general population.

4.5 To assess whether CRC screening using various types of IFOBT have issues related to the ethical, legal, and organizational aspects.

5.0 METHODS

5.1. Literature search strategy

Literature search was done by two Information Specialists who searched for published articles pertaining to the use of IFOBT for CRC screening. The following electronic databases were searched: MEDLINE (1950-Week 1 June 2011), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to May 2011), EBM Reviews-Cochrane Central Register of Controlled Trials (2nd Quarter 2011), EBM Reviews-HTA Databases (2nd Quarter 2011), EBM Reviews-Cochrane Methodology Register (2nd Quarter 2011), EBM Reviews-ACP Journal Club (1991 to May 2011), EBM Reviews-NHS Economic Evaluation Database (2nd Quarter 2011) via OVID, PubMed, INAHTA database, HTA database and US FDA database. The last search was run on 10 August 2011. No limits were applied to the search. Detailed search strategy is as in Appendix 4. Additional articles were identified from reviewing the bibliographies of retrieved articles and hand-searching of journals. General search engine was used to get additional web-based information.

5.2. Study selection

Based on the policy question the following inclusion and exclusion criteria were used:-

5.2.1 Inclusion criteria

a.	**Study design**	Cross-sectional diagnostic accuracy studies, HTA reports, systematic review, randomised controlled trial (RCT), cohort, case-control, and economic evaluation studies.
b.	**Population**	Adults, general population
c.	**Intervention**	Various types of IFOBT
d.	**Comparator**	i. No comparator ii. Faecal DNA testing
e.	**Outcomes**	i. Primary outcome: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) ii. Mortality, incidence rate, detection rate iii. Adverse events related to the use of IFOBT for CRC screening iv. Cost, cost-benefit, cost-effectiveness, cost utility, and economic evaluation of using IFOBT
f.	**Publication**	English full text articles

5.2.2 Exclusion criteria

i. Animal study
ii. Narrative review
iii. Laboratory study
iv. Non English full text articles

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it is absolutely clear from the title and/or the abstract that the study was not relevant, it was excluded. If it was unclear from the abstract and/or the title the full text article was retrieved. Two reviewers assessed the content of the full text articles. Disagreement was resolved by discussion.

5.3 Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool depending on the type of study design.[13] Quality assessment was conducted by two reviewers. Disagreements were resolved by discussion. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1) or NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4(2nd Edition), March 2001 for test accuracy studies (Appendix 2).[14, 15]

5.4 Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 6) and checked by another reviewer. Disagreements were resolved by discussion and the extracted data was presented and discussed with the expert committee. The data extracted was as follows:-

5.4.1 Details of methods including study design.

5.4.2 Study population characteristics including age, trial inclusion and exclusion criteria.

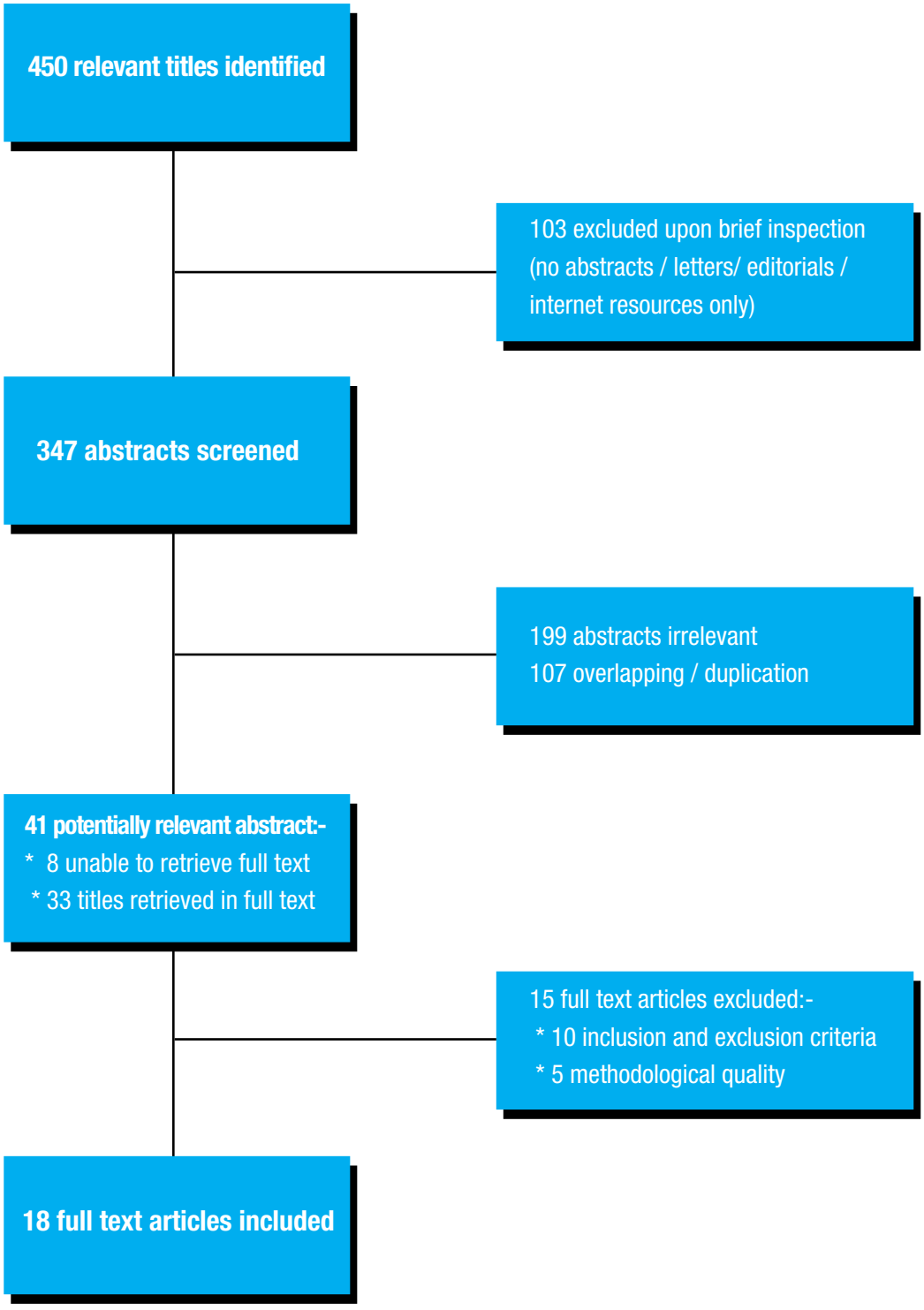
5.4.3 Details of intervention and comparator.

5.4.4 Types of outcome measures including diagnostic accuracy of the various types of IFOBTs (sensitivity, specificity, PPV, and NPV), effectiveness of CRC screening using various types of IFOBTs (mortality, incidence rate, detection rate), adverse events related to the use of IFOBT, cost, cost-benefit, cost-effectiveness, cost utility, and economic evaluation of using IFOBT, and any information on ethical, legal and organizational aspect related to CRC screening using various type of IFOBT.

6.0 RESULTS

Search strategies yielded many published articles related to IFOBT for CRC screening. A total of 450 relevant titles were identified and 347 abstracts were screened using the inclusion and exclusion criteria. Of these, 199 abstracts were found to be irrelevant and 107 abstracts overlapping/duplication. Forty-one potentially relevant abstracts were attempted for retrieval. Of these, 33 potentially relevant articles were retrieved in full text, and full text for eight abstracts cannot be retrieved. After reading and appraising the full text articles, 18 full text articles were included, as shown in Figure 4. Fifteen full text articles were excluded based on inclusion and exclusion criteria, and quality of the studies are listed in Appendix 7. The articles comprised nine cross-sectional diagnostic accuracy studies, two cohort studies, two case-control studies, and five economic evaluation papers. We also included one article by the World Health Organization (WHO).

Figure 4: Flow chart of retrieval of articles used in the results



6.1 DIAGNOSTIC ACCURACY AND EFFECTIVENESS

6.1.1 Diagnostic accuracy of IFOBT and factor effecting

There was limited evidence available from studies on the diagnostic accuracy of various IFOBTs used, and that there were no RCTs evaluating diagnostic performance.

There was a study comparing the qualitative and quantitative IFOBT for CRC screening. Castiglione G *et al.* (2000) compared the performance of two IFOBTs, Immudia Hem-Sp or Hemeselect (RPHA) with the OC-Hemodia (LAT), the latter was developed by a completely automated procedure provided by the manufacturer and interpreted according to three positivity thresholds: 100 ng (Hdia100), 150 ng (Hdia150), or 200 ng (Hdia200) of haemoglobin/ml of the specimen solution. Both tests were completed by 5,884 average risk participants (2,997 women, mean age 59.6 years and 2,867 men, mean age 59.5 years) in a population-based screening programme, in 28 municipalities of the Province of Florence, Italy. The participants were instructed to collect faeces samples using RPHA cards and Hdia sticks on a single bowel movement and returned kits as soon as possible after faeces collection. No dietary restriction was required.

Participants with positive IFOBT results were then invited to undergo colonoscopy with biopsy or a combination of partial colonoscopy and DCBE when colonoscopy is impossible. Positivity rates and PPV for CRC or high risk adenomas were calculated for each test and then compared. High risk adenoma (HRA) was assumed to be present in those with adenoma/s larger than 9 mm or who presented with villous or tubulovillous pattern, or severe dysplasia. The study found that for RPHA, positivity rate was higher (3.3%, 95% Confidence interval, CI: 2.9% to 3.8%) compared to Hdia150 (2.5%, 95% CI: 1.5% to 4.3%) and Hdia200 (2.0%, 95% CI: 1.3% to 4.1%), but slightly lower when compared to Hdia100 (3.5%, 95% CI: 3.1% to 4.0%). However, there was no significant difference between tests was found for the PPV for CRC or adenomas. The authors concluded that Hdia100 was as sensitive as RPHA for cancer and HRA, and increasing the positivity threshold of Hdia up to 150 ng and 200 ng of haemoglobin/ml of specimen solution is not advisable.[16 level 3]

A recent study by Castiglione G *et al.* (2002) interpreted the overall experience with OC-Hemodia (LAT), which developed with OC-Sensor, a fully automated analyzer. A population-based screening programme involved subjects aged 50 to 70 years, invited every two years to have an IFOBT in Florence, Italy. A total of 11,774 subjects attended screening for the first time (6,063 women, mean age 59.1 years and 5,711 men, mean age 59.2 years); and 7,358 at subsequent screening (3,746 women, mean age 60.5 years and 3,612 men, mean age 60.8 years). Subjects who agreed to perform the OC-Hemodia (LAT) collected faecal samples by means of the stick provided by the manufacturer. The returned specimens were stored at 2 to 10° Celcius and assayed within one week of collection in laboratory by a completely automated analyzer. In their preliminary study and the current study, only tests with concentration of 100 ng haemoglobin/ml sample solution or higher were considered positive and the subjects were invited to undergo colonoscopy with biopsy or a combination of partial colonoscopy and DCBE. Subjects with negative IFOBT were invited to repeat screening after two years and to visit their general practitioners (GP) for any bowel complaint occurring in the interval between screenings. Performances of the test were interpreted with 11 positivity thresholds put at every 10 ng/ml intervals between 100 ng/ml and 200 ng/ml. Progressively increasing the positivity threshold from 100 ng/ml to 200 ng/ml showed:

i. A decreased in positivity rates from 4.2% to 2.4% and from 3.4% to 1.6% in first and subsequent screening, respectively.

ii. A decrease in detection rates for CRC (3.3‰ to 2.7‰) or HRAs (7.9‰ to 5.9‰) in first screening; and 1.6‰ to 1.4‰ for CRC or 4.9‰ to 2.3‰ for HRAs in subsequent screening.

iii. An increase in PPV for cancer from 9.0% to 13.4% and from 5.5% to 10.9% in first and subsequent screening, respectively.

iv. An increase in PPV for HRAs from 21.3% to 28.9% and from 16.6% to 18.5% in first and subsequent screening, respectively.

The authors concluded that increasing the positivity threshold of the OC-Hemodia (LAT) reduces recall rate and improve PPV for cancer or HRAs but substantially decreases the detection rate of CRC and HRAs. For this reason increasing the positivity threshold is not advisable. On the other hand decreasing the positivity threshold would increase recall rate and sensitivity of screening.[17 level 3]

A cost-effectiveness and diagnostic validity study by Nakama H, Zhang B, and Zhang X in 2001 assessed the optimum cut-off point of faecal haemoglobin (50 ng/ml, 150 ng/ml, and 300 ng/ml) using OC-Hemodia, which interpreted using OC-Sensor, a fully automated analyzer. A total of 4,260 asymptomatic people aged over 40 years who participated in a medical check-up for CRC between April 1990 and March 1999 served as subjects of this study. Four samples of two consecutive days stool from each subject were tested without dietary or medicinal restriction. Faecal smears from the subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received a colonoscopy examination with biopsy. Accordingly, the sensitivity and specificity were reported as:

i. 24/27 (89%) and 3,979/4,233 (94%) for the 50 ng/ml level
ii. 22/27 (81%) and 4,080/4,233 (96%) for the 150 ng/ml level
iii. 15/27 (56%) and 4,109/4,233 (97%) for the 300 ng/ml level

There was a significant difference in the sensitivity between the 50 ng/ml level and 300 ng/ml level ($p<0.05$) as well as between the 150 ng/ml level and 300 ng/ml level ($p<0.05$), and a significant differences in the specificity between the 50 ng/ml level and 300 ng/ml level ($p<0.05$). However, no significant difference was observed in the specificity between the 50 ng/ml level and 150 ng/ml levels. The findings indicated that the cut-off point of 150 ng/ml faecal haemoglobin was recommended for IFOBT by OC-Hemodia.[18 level II-3]

Li SC *et al.* (2007) conducted an analysis to determine the optimal cut-off point of IFOBT (brand names not stated) for population-based CRC screening in Taiwan, by using receiver operating characteristics (ROC) curves. Data used for producing ROC curve analysis were derived from 56,968 subjects (including 21,502 men and 35,466 women). Out of 56,968 subjects, 22,672 subjects aged 50 years or older were invited annually to have an uptake of IFOBT (58.0% were woman). The mean age was 63.36 ± 9.20 years. Two stage screening procedure was used to ascertain asymptomatic adenoma and invasive carcinoma of the colon and rectum. One day IFOBT method with a brush type sampler was given to each eligible subject while he/she was invited to out-reaching screening. The participants returned the collected stool sample within three to five days to each health centre in the vicinity where the screening activity was held. The stool sample was uploaded to the automated machine to yield a series of quantitative readings of IFOBT value. All subjects with IFOBT levels ≥ 100 ng/ml were defined as having positive IFOBT. From the ROC curve analysis, the area under curve was 0.87 (95% CI: 0.81 to 0.93). The optimal cut-off was 100 ng/ml at which the corresponding sensitivity, false positive and odds of being affected given a positive result (OAPR) for detection of CRC were 81.5% (95% CI: 70.2% to 89.2%), 5.7% (95% CI: 5.4% to 6.0%), and 1.24 (95% CI: 1.19 to 1.32), respectively.[19 level II-3]

In 2004, Crotta S *et al.* performed a pilot study in two municipalities of the region Valle d'Aosta, with the aim of evaluating the feasibility of a regional screening programme for CRC using IFOBT. The IFOBT used was based on OC-Hemodia (LAT), which interpreted using OC-Sensor, a fully automated analyzer. A total of 2,961 subjects (1,403 males and 1,558 females) aged 50 to 74 years were invited by mail to perform a one-day IFOBT without any dietary restrictions and with a positive threshold put at 100 ng/ml. Patient with positive tests were then invited to undergo colonoscopy with biopsy and DCBE if colonoscopy was incomplete. Patient with negative tests were suggested to repeat screening after two years and to visit their GP with any bowel complaint occurring during that period. The study revealed that out of 1,631 patients who performed the screening test, 72 (4.4%) had a positive IFOBT and 67 of which 72 patients (93.1%) agreed to undergo colonoscopy. Positive predictive value (PPV) for cancer and adenomas were 4.5% and 40.3%, respectively. The authors concluded that the use of a one-day quantitative latex IFOBT with no dietary restriction, automation of the analytical procedure, and a positive threshold of 100 ng/ml has shown that a programme based on this test is feasible in both organizational and attendance terms.[20 level 3]

An observational prospective study was carried out by Fenocchi E *et al.* (2006) in Uruguay to evaluate the feasibility of CRC screening using IFOBT. A total of 11,734 (3,663 men, mean age 61.3 ± 9.6 years and 8,071 women, mean age 61.2 ± 9.1 years) volunteers were enrolled in the CRC screening programme. Each volunteer received one IFOBT kit (OC-Hemodia) to be used at home on a single day and returned the samples to the centre in a cold box. An automated system (OC-Sensor II) was used for processing the samples with a 100 ng/ml cut-off haemoglobin level. Only participants with positive IFOBT results were offered a video colonoscopy with biopsy. The study showed that out of 11,734 study participants who received an IFOBT test kit, 10,573 (90.1%) returned samples for screening. The results of 1,170 (11.1%) of the responders were positive. Subsequently, colonoscopy was performed on 879 (75.1%) of the participants with a positive test results and showed neoplasia in 330 participants. They reported PPV of 8.6% and 11.2% for cancer and HRA, respectively. The authors concluded that the high compliance and high detection rates for cancer and HRA achieved in the CRC screening programme verifies the feasibility of an IFOBT in screening an average risk population in Uruguay.[21 level 3]

A study by Rubeca T *et al.* (2006) was conducted to compare the diagnostic efficacy of a recently commercialized IFOBT assay (FOB Gold, Sentinel = SENT) compared to the assay currently employed in the Florence screening program (OC-Hemodia, which developed with OC-Sensor, a fully automated analyzer). A total of 4,133 subjects (2,117 women and 2,016 men, age range between 50 to 69 years) from three municipalities of the Florence district were invited to participate in the study. They were provided with OC and SENT kits and were asked to perform both samplings on the same bowel movement. No dietary restrictions were prescribed. Test tubes were delivered to the lab within two days of sampling and stored at 2 to 8°C before processing. Subjects with a positive IFOBT results (100 ng/ml haemoglobin cut-off) were referred for total colonoscopy with biopsy and DCBE when colonoscopy was incomplete. The study indicated that the PPV for cancer was 5.0% for OC and 3.8% for SENT. The PPV for CRC+HRA was 31.4% for OC and 28.2% for SENT. The specificity for CRC+HRA was 97.7% for both methods. Based on finding, the authors concluded that SENT assay is less sensitive than OC assay for CRC and HRA, but since the observed difference did not reach statistical significance, further study were needed for confirmation; also needed is a detailed study of the analytical aspects in order to investigate intrinsic accuracy differences between the two assays.[22 level 3]

Morikawa T *et al.* (2007) conducted a cross-sectional study to investigate the sensitivity of IFOBT with special attention to small adenomas (≤ 9 mm), using a large-scale cohort of patients who underwent colonoscopy and IFOBT. A total of 21,805 subjects (15,694 males and 6,111 females; mean age 48.2 ± 9.3 years) completed the protocol of undergoing IFOBT and colonoscopy examination with biopsy. All eligible subjects were asymptomatic and participated voluntarily. They performed a one-day IFOBT which participants were asked to prepare a faecal sample from a stool specimen using a collection kit provided by manufacturer. The participants then brought the collection tubes to the hospital or clinic on the day of colonoscopy, and the samples were sent to the laboratory within 24 hour for immediate testing using Magstream 1000/Hem SP, an automated analyzer for IFOBT. The study showed that the sensitivity to adenomas ≤ 9 mm was significantly higher than the false positive rate as revealed by analysis of all eligible subjects (7.0% versus 4.5%, $p<0.001$). Subanalysis of the sensitivity to small adenomas according to patient age and gender revealed that the test was more sensitive in men than in women, and that the sensitivity increased as subjects aged (6.1% in men < 50 year and 11.3% in men > 60 year). In women, on the other hand, the sensitivity to small adenomas was not significantly higher than the false positive rate in any generation (5.1% versus 4.7% for all eligible women, $p=0.72$). The authors made a conclusion that IFOBT detected a small percentage of small adenomas at a rate that is significantly higher than the false positive, at least in male patients. However, clinical relevance of small adenomas is still controversial and therefore comparative studies between gFOBT and IFBOT with the end point of CRC-related death are expected.[23 level 3]

A cost-effectiveness and diagnostic accuracy study was carried out by Nakama H, Zhang B, and Fattah ASMA in 2000 to assess, the optimum number of faecal specimens to collect for use in IFOBT as a means of screening for CRC. A total of 3,300 asymptomatic people aged over 40 years who participated in a medical check-up for CRC served as subjects of this study. The six samples of three consecutive days' stool from each subject were tested by a qualitative IFOBT Monohaem, without dietary or medical restriction according to the test principle. Faecal smears from the subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received colonoscopy examination with biopsy. For evaluation of the optimum number of sampling specimens, the results of the first day of sampling, those of the first and second day, and those of samples taken for three consecutive days were considered as the single-day method, the two-day method and the three-day method, respectively. The study revealed that 17 patients with CRC were diagnosed by colonoscopy. Positive cases of an IFOBT were 125 (3.8%), 168 (5.1%), and 191 (5.8%) in the single-day, two-day and three-day methods. The numbers of patients with CRC detected by colonoscopy examination were eight, 14 and 15 in the single-day, two-day and three-day methods. Accordingly, the detection rate and the false positive rate were reported as:

i. 47% and 3.5% for the single-day method of collection
ii. 82% and 4.7% for the two-days method
iii. 88% and 5.3% for the three-day method

There was a significant difference in the detection rate between the single- and two-day methods ($p<0.05$) and between the single- and three-day methods ($p<0.05$). There was no significant difference in the detection rate and false positive rate between the two-day and three-day methods. The authors concluded that the two-day faecal collection method is recommended for IFOBT by Monohaem.[24 level II-3]

Pertinent details of the included diagnostic accuracy studies are provided in Appendix 8.

6.1.1a Effect of variation in ambient temperature on IFOBT

Immunochemical faecal occult blood test (IFOBT) detects the intact globin moiety of human haemoglobin or its early degradation products, but little is known about its stability under different storage conditions. A recent study by Grazzini *et al.* (2010) is the first to describe a relationship between the seasons and the haemoglobin concentrations measured in faecal samples in a screening programme for CRC. The aim of the study was to examine the performance of IFOBT (OC-Sensor Micro instrument) in the Florence screening programme over several seasons to evaluate the impact of variations in ambient temperature on the performance of the screening test. A total of 199,654 IFOBT (93,191 men and 106,463 women) were performed in the CRC screening programme. Participants in the screening programme received detail written and oral information about preparing faecal samples and were asked to return the test samples as soon as possible in order to avoid degradation of haemoglobin. Subjects who tested positive were offered a full colonoscopy with biopsy during dedicated sessions at an accredited assessment clinic. Measured haemoglobin concentration was aggregated into seasons with their average ambient temperature (AAT). Using logistic regression, the AAT over the period preceding the test measurement was analysed. This period included the time between faecal sampling and return of the test sample (mean seven days) and the time in the laboratory refrigerator before analysis (mean four days). The AAT from day five to 11 before analysis of the test sample was considered a determinant of test positivity. A non-parametric test (Kruskal-Wallis rank test for quality) was used to evaluate the difference across the seasons. The probability of the IFOBT being positive (haemoglobin concentration ≥ 100 ng/ml) and of diagnosing a neoplastic lesion (cancer or advanced adenoma) was studied using a logistic model adjusted for sex, age, season and episode of screening (first or repeated test). The study revealed that mean IFOBT seasonal haemoglobin concentration were:

i. 27.6 ng/ml in spring (95% CI: 26.2 to 29.1)
ii. 25.2 ng/ml in summer (95% CI: 23.1 to 27.3)
iii. 29.2 ng/ml in autumn (95% CI: 27.2 to 30.6)
iv. 29.5 ng/ml in winter (95% CI: 27.9 to 31.1)

The results of the logistic regression showed that there was a 17.0% lower probability of the IFOBT being positive in summer than in winter. An increased in temperature of 1.0°C produced a 0.7% reduction in probability of an IFOBT being positive. In the summer the probability of detecting a cancer or an advanced adenoma was about 13.0% lower than in the winter. They concluded that there was a significant fall in haemoglobin concentration at higher ambient temperatures. The observations described in this study need to be confirmed by other programmes working under a variety of different climatic conditions.[25 level II-2]

6.1.1b Effect of delayed sample return

IFOBT performed at home by screening participants are promising in population-based screening for CRC. Some IFOBT's are quantitative, and the faecal sample is stored in a sample bottle containing haemoglobin stabilizing buffer. However, the stability of faecal haemoglobin in the stabilizing buffer has not been studied comprehensively. Several factors may influence haemoglobin stability such as storage conditions and lag time before the faecal sample is analyzed. Delayed return of IFOBT samples to a laboratory might cause false negative because of haemoglobin degradation.

Therefore, van Rossum LGM *et al.* (2009) studied the effect of delay between sampling and laboratory delivery on IFOBT (OC-Sensor Micro instrument) performance. A large prospective population-based screening study in more than 20,000 persons in Netherlands (aged 50 to 75 years) was performed from June 2006 to February 2007. Half of the screening population was randomly allocated to receive an IFOBT. Participants performed the sampling for the test at home and were instructed to return the test as soon as possible by mail. They were asked to report the date of faecal sampling on the sample tube. IFOBT positivity threshold (≥ 50 ng/ml haemoglobin) in CRC screening participants without delay (< 5 days) was compared with positivity in participants with ≥ 5 and ≥ 7 days delay. Only patients with an IFOBT positive result went for colonoscopy with biopsy. The OR and 95% CI were presented for the difference between participants with delay compared with participants without delay. Odds ratio was corrected for age, gender and place of residence with multivariate logistic regression analysis. Additionally, positive tests were stored at room temperature and retested five times within 10 to 14 days. They measured the mean and the median decreased of faecal haemoglobin in the sample solution over time and estimated the risk of false negative due to degradation of faecal haemoglobin (< 50 ng/ml). The study showed that OC-Sensor tests were positive (≥ 50 ng/ml) in 265/3062 (8.7%) of tests delivered without delay, in 42/705 (6.0%) with a delay ≥ 5 days and in 8/195 (4.1%) with a delay ≥ 7 days. Compared with OC-Sensor tests returned without delay, the positivity rate was significantly decreased after a delay ≥ 5 days (OR 0.7; 95% CI 0.5 to 0.9), and after a delay ≥ 7 days (OR 0.5; 95% CI 0.2 to 0.9). Of the 170 participants positive OC-Sensor tests (≥ 50 ng/ml) 139 (82%) had a colonoscopy with biopsy. They found that 45/139 (32.4%) had advanced adenomas and 8/139 (5.8%) had CRC. In patients with advanced adenomas, haemoglobin in the sample was < 50 ng/ml in 5/45 (11.1%) two to three days after the initial test and in 16/45 (35.6%) after 10 to 14 days. Only after seven days, 2/8 (25.0%) of the samples of participants with CRC became false negative.

The authors concluded that the performance of the IFOBT (OC-Sensor Micro instrument) was decreased by delay in time between faecal sampling and laboratory delivery. Later stage CRC patients will probably not be missed due to this delay, but at least a relevant proportion of patients with advanced adenomas and possibly stage I CRC might be missed even with a delay of a few days. Until a less sensitive haemoglobin stabilizing buffer is produced, monitoring delay between faecal sampling and laboratory research should be part of quality control for screening with IFOBT. Inviting participants to perform a second test when delay is ≥ 5 days could be considered.[26 level 3]

6.1.2 Colorectal cancer (CRC) mortality

Saito H *et al.* (1995) conducted a case-control study to evaluate the reduction in risk of mortality from CRC by faecal occult blood screening using qualitative single-day immunochemical hemagglutination test. This test (Immudia-Hem Sp or HemeSelect) has been performed since 1986 in Aomori Prefecture. The entire population of the 26 study areas combined was 296,439 (154,715 males and 141,724 females) at the time when the screening program was started. Case subjects are defined as those who:

i. Died of CRC during the period between April 1, 1986 and December 31, 1992

ii. Were diagnosed as having CRC between the ages of 40 and 79 after the screening program was started

iii. Had been living in the same area since the screening program was started

iv. Had not had previous histories of CRC before the screening program was started in 1986 or 1987

Three controls were randomly selected from the list of individuals who were alive at the time of diagnosis of the corresponding case and had been living in the same area as the case, matched by gender and age. Conditional logistic regression analysis was used to calculate the OR of dying of CRC for those screened within one to five years before case diagnosis versus those not screened in the corresponding intervals. Odds ratio (OR) was also calculated by number of years since the most recent screening history, to study the optimal screening interval. A total of 193 cases and 577 controls were used in the analysis. The study revealed that the risk of developing fatal CRC was reduced by 23% to 60% among those who had a screening history, relative to those not screened. The OR for those screened within one, two and three years of case diagnostic versus those not screened were 0.40 (95% CI: 0.17 to 0.92), 0.41 (95% CI: 0.20 to 0.82), and 0.48 (95% CI: 0.25 to 0.92), respectively. Based on the findings, the results suggested that CRC screening by the IFOBT would reduce mortality from CRC.[27 level II-2]

6.1.3 Detection of precancerous lesions and advanced CRC

Yang H *et al.* (2011) evaluated the effectiveness of IFOBT for the screening of precancerous lesions and CRC. Immunochemical faecal occult blood test (IFOBT) was performed on 5,919 adults (3,268 men and 2,651 women; mean age 55.18 ± 15.67 years) who received periodic health examination in the health care centre of Renji Hospital, Shanghai. The exclusion criteria were as follows: cases with gingival haemorrhage, epitasis, menses, anal fissure, haemorrhoid, and other diseases that could influence the test result; patients who were reluctant to provide faecal samples; and patients who refused colonoscopy and/or DCBE examinations. The test was performed using an OC-MICRO™ instrument and the positivity threshold was set at 100 ng/ml of haemoglobin. Diagnosis was confirmed by histopathological analysis which all pathologists were blinded to the IFOBT results. From the study, 314 out of 5,919 adults screened were found to be positive (5.3%), whereas 201 cases (64.0%) were male and 113 cases (35.9%) were female. Further examination was made in 264 IFOBT positive cases. Out of the 264 cases investigated, 116/264 (43.9%) were found to have CRC (16 cases) and precancerous lesions (94 cases with colorectal adenomatous polyps and six cases with active ulcerative colitis). The TNM classification of 16 CRC cases was as follows: TNMI in eight cases (50.0%), TNMII in seven cases (43.8%), and TMIII in one case (6.3%), indicating IFOBT can detect CRC in the early stages. The authors concluded that regular IFOBT can detect precancerous lesions and CRC in early stages and can thus reduce mortality from CRC.[28 level 3]

A case-control study was conducted by Nakajima M *et al.* (2003) to evaluate whether screening with the IFOBT reduces the risk of developing advanced CRC in the area where annual screening with the IFOBT has been performed. CRC screening has been conducted using single-day IFOBT test (Immudia-Hem Sp) since 1986 in Aomori Prefecture. Screening was annually offered to all men and women, who held national health insurance, aged ≥ 40 years. Screeners who tested positive for FOBTs were recommended to undergo diagnostic investigation by total colonoscopy with biopsy. Cases were defined as the consecutive patients clinically diagnosed as having advanced CRC that invaded to the muscularis propriae or deeper, which required surgery. For inclusion, case subjects were ≥ 40 years at the time of diagnosis and had been living in the same area since 1986 when the screening programme was started. Patients with a previous history of CRC were excluded. Potential case subjects were obtained from the files of cancer registries that cover the whole prefecture. Diagnoses of CRCs were scrutinised by reviewing medical records for colonoscopic and/or radiographical findings, anatomic location of the cancer, histological diagnosis and depth of cancer invasion. For each case, three controls were randomly selected from the list of residents in 1986 in the study area, where the corresponding case lived, matched by gender, and residential area within the town or village.

Conditional logistic regression analysis was used to calculate the OR of developing advanced cancer for those having at least one screening test within two, three, four and five years before case diagnosis versus those having no screening test in the corresponding periods. The OR was also calculated for those having their most recent screening history in each of the two to five years, to study the optimal screening interval. A total of 375 cases and 1,065 controls were used in the analysis. The study demonstrated that the risk of developing advanced CRC was reduced by 28% to 46% among individuals having at least one screening within two to four years before case diagnosis. The OR for those screened within two and three years before the diagnosis versus those not screened was 0.60 (95% CI: 0.29 to 1.23) and 0.54 (95% CI: 0.29 to 0.99), respectively. However, no reduction in risk was observed after more than three years. Regarding the anatomical location, the OR of developing advanced cancer for those having at least one screening history within two to five years was lower for the rectum than for the colon (OR: 0.32 to 0.73 and OR: 0.84 to 1.18 for rectum and colon, respectively). These results suggested that a screening programme with IFOBT can be effective for prevention of advanced CRC. However, risk reduction appears to be larger for the rectal than for colon cancer.[29 level II-2]

6.1.4 Interval cancer

Interval cancer (IC) is defined as cancers that are detected after a negative screening episode and before the next invitation for screening. The IC rates is one of the most important early indicators of screening efficacy for monitoring screening programme quality and its potential impact on cancer mortality.

Zorzi M *et al.* (2010) conducted a cohort study to estimate the test and episode sensitivity of five CRC screening programmes taking place in the Veneto Region, Italy through the identification of ICs obtained by the linkage of screening archived and hospital discharge records (HRDs). Interval cancer were identified in subjects who had a negative result in a screening examination from 2002 to 2007 (n=267,769). Out of total 267,769 subjects, 173,859 were a first screening and 93,010 a subsequent. The data were linked with 2002 to 2008 HDRs. Analysis was based on the follow up of 468,306 person-years. Two latex agglutination test were used (OC-Hemodia, developed with the OC-Sensor Micro instrument) in four programmes and FOB Gold in one programme, with a positivity threshold of 100 ng/ml of sample solution. Colonoscopy with biopsy (or, when a complete colonoscopy is not possible, a DCBE x-ray) was recommended to all IFOBT positive subjects. The proportional incident-based sensitivity was estimated overall and by sex, age class, time since last negative IFOBT result, anatomical site, and history of screening (first or subsequent test). The results of the study showed that 748 cancers were detected at screening with a detection rate of 2.8 per 1,000 screened.

Overall, 126 ICs were identified, compared to 572 expected cancers. The proportional incidences were 15.3% and 31.0% in the first and the second interval years, respectively, with an overall episode sensitivity of 78.0% (95% CI: 73.8% to 81.6%). Sensitivity was higher for males than females (80.1% versus 74.8%), and no differences were observed by age, anatomical site or between programmes. The test sensitivity of IFOBT was 82.1% (95% CI: 78.1% to 85.3%). The authors concluded that IFOBT-based screening programmes showed a high performance in terms of sensitivity as estimated through the IC rates. The screening schedule utilised in the programmes (single IFOBT, positivity threshold of 100 ng/ml of sample solution, inter-screening interval of 2 years) shows low rates of missed cancers that are diagnosed during the interval.[30 level II-2]

6.2 SAFETY

There was no retrievable evidence from the scientific databases on adverse events associated with IFOBTs used for CRC screening. The use of IFOBTs in a screening setting is likely to increase the number of colonoscopies, sigmoidoscopies and DCBE performed in the screened population. It is expected that the adverse events associated with these procedure will also be increased. Several test methods on IFOBT that had been approved by the US FDA and are currently available in the United States are shown below: [31]

i. Hemoccult® ICT (Beckman Coulter, Inc.)
ii. FlexSure® OBT (Beckman Coulter, Inc.)
iii. Instant-View® FOBTII (Alpha Scientific Designs, Inc.)
iv. InSure® (Enterix, Inc.)
v. ImmoCARE® (Care Products, Inc.)
vi. Hemeselect® (Fujirebio)
vii. Immudia Hem-Sp® (Fujirebio)
viii. Monohaem® (Nihon Pharmaceuticals, Japan and Chemicon International, Inc., Australia)

6.3 COST/COST-EFECTIVENESS/ECONOMIC EVALUATION

The optimum number of faecal specimens to collect for use in IFOBT as a means of screening for CRC was conducted by Nakama H, Zhang B, and Fattah ASMA in 2000. A total of 3,300 asymptomatic people aged over 40 years who participated in a medical check-up for CRC served as subjects of this study. The six samples of three consecutive days' stool from each subject were tested using a qualitative IFOBT Monohaem, without dietary or medical restriction according to the test principle.

Faecal smears from the subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received colonoscopy examination with biopsy. For the evaluation of the average costs per detection of one CRC case amongst the three faecal sample collection methods, they used the results of the first day to denote a single-day faecal collection method, the results of the first and second days as a two-day faecal collection method and the results of the three consecutive days as a three-day faecal collection method. The study reported that the average costs per case detected were USD$3,360.68 for the single-day method, USD$3,350.65 for the two-day method and USD$4,136.36 for the three-day method, respectively as shown in Table 2.

Table 2: Comparison of the average costs per patient with CRC detected for the three faecal collection methods of immunochemical faecal occult blood screening

	Faecal collection methods		
	Single-day	2-day	3-day
I. Screening costs (A×B)	$12 000.00	$24 000.00	$36 000.00
A. Faecal occult blood test	$3.64 (¥400)	$7.27 (¥800)	$10.91 (¥1200)
B. No. of patients screened	3300	3300	3300
II. Examination costs (A×B)	$17 045.45	$22 909.09	$26 045.45
A. Diagnostic examination	$136.36 (¥15 000)	$136.36 (¥15 000)	$136.36 (¥15 000)
B. No. of patients examined	125	168	191
III. Total costs (I+II)	$29 045.45	$46 909.09	$62 045.45
IV. No. of detected cancers	8	14	15
V. Average costs per case detected (III/IV)	$3630.68	$3350.65	$4136.36

The average costs calculated in this study showed that the two-day testing method was the least expensive (USD$3,350.65) and was therefore recommended as the optimum cost-effective approach for immunochemical faecal occult blood screening by Monohaem.[24]

A cost-effectiveness and diagnostic validity study by Nakama H, Zhang B, and Zhang X in 2001 assessed the optimum cut-off point of faecal haemoglobin (50 ng/ml, 150 ng/ml, and 300 ng/ml) using OC-Hemodia, which interpreted using OC-Sensor, a fully automated analyzer. A total of 4,260 asymptomatic people aged over 40 years who participated in a medical check-up for CRC between April 1990 and March 1999 served as subjects of this study. The four samples of two consecutive days stool from each subject were tested, without dietary or medicinal restriction. Faecal smears from the subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received a colonoscopy examination with biopsy. The costs of IFOBT as well as colonoscopy procedure were calculated.

The average cost to detect one patient with CRC of these three cut-off point of faecal haemoglobin were evaluated. The study showed that the average costs for the detection of one cancer case were USD$2,870.45 for the cut-off point of 50 ng/ml level, USD$2,492.98 for the 150 ng/ml level and USD$3,329.09 for the 300 ng/ml level, respectively as shown in Table 3.

Table 3: Comparison of the average costs per patient with CRC detected for the three cut-off points of faecal haemoglobin in the immunochemical faecal occult blood screening

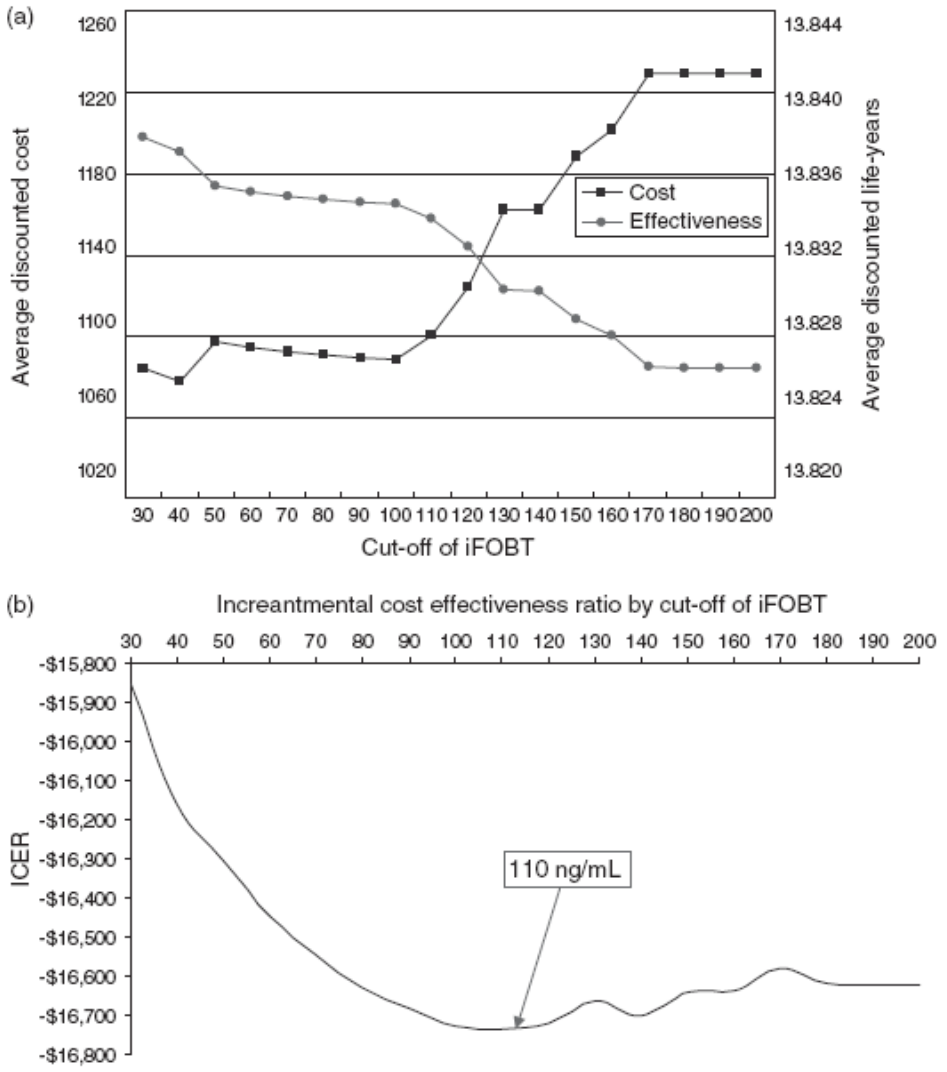
	Cut-off points		
	50 ng/ml	150 ng/ml	300 ng/ml
I. Screening costs (A×B)	$30981.82	$30981.82	$30981.82
A. Fecal occult blood test	$7.27 (¥800)	$7.27 (¥800)	$7.27 (¥800)
B. No. of patients screened	4260	4260	4260
II. Examination costs (A×B)	$37909.09	$23863.64	$18954.55
A. Diagnostic examination	$136.4 (¥15000)	$136.4 (¥15000)	$136.4 (¥15000)
B. No. of patients examined	278	175	139
III. Total costs (I+II)	$68890.91	$54845.46	$49936.37
IV. No. of cancers detected	24	22	15
V. Average costs per case detected (III/IV)	$2870.45	$2492.98	$3329.09

The findings indicated that the cut-off point of 150 ng/ml faecal haemoglobin is recommended for IFOBT by OC-Hemodia, from the viewpoints of cost-effectiveness, as well as diagnostic validity.[18]

Li SC *et al.* (2007) conducted a cost-effectiveness analysis for determining optimal cut-off point of IFOBT (brand names not stated) for population-based CRC screening in Keelung Community-based Integrated Screening (KCIS) Taiwan. The optimal cut-off was first determined by receiver operating characteristics (ROC) curves analysis. Economic evaluation (Markov decision model and Markov cohort simulation) was further applied to identifying the optimal cut-off by assessing the minimum incremental cost-effectiveness ratio (ICER), an indicator for cost per life year gained (effectiveness), given a series of cut-offs of IFOBT, ranging from 30 ng/ml to 200 ng/ml compared with no screening. The model had a hypothetical cohort from people aged 50 to 80 years with population size and the make-up of demographic characteristic identical to subjects in the screening programme. The economic analysis (Figure 4a) shows the relationship between average discounted life years and discounted costs and different cut-offs of IFOBT. The average discounted life years decreased with the increased cut-off of IFOBT. Figure 4b shows the corresponding results of ICER. For 'no screening' (the baseline group), the average discounted life years and costs were 13.7797 and 2005.40. Compared with the baseline group, the screening programme irrespective of any cut-off dominated over the control group indicated by minus ICER (less cost and more effectiveness).

Given 100% attendance rate, ICER had the lowest value at 110 ng/ml at which average discounted life years and costs were 13.83 and 1100.10, which yielded an average of 0.054 life year gained and that of cost-saving by 905.30 (USD$). Based on analysis, the optimal cut-off value recommended for subjects aged 50 years or older in this community-based screening programme was 110 ng/ml. Their model provides a useful approach for health policy-makers in designing population-based screening for CRC to determine the optimal cut-off of IFOBT when cost and effectiveness need to be taken into account. However, the authors strongly stated as its limitation that their cost-effectiveness analysis findings is inadequate for other population-based screening excepted for the KCIS, Taiwan.[19]

Figure 4: The change of average discount cost (USD$) and life years and ICERs by cut-off values of IFOBT



Telford J *et al.* (2010) conducted a cost-effectiveness study to estimate the incremental cost-effectiveness of 10 strategies for CRC screening, as well as no screening program (Markov model), in 50-year-old individuals at average risk for CRC. Screening and surveillance continued until 75 years of age, and the analysis continued through the lifetime of the cohort. They populated the model with data from the published literature and calculated costs from the perspective of a third-party payer, with inflation to 2007 Canadian dollars. The model output was quality-adjusted-life-years. They discounted costs and effects at 5.0% annually and used a half-cycle correction to account for these discounts. This study focuses on the comparison of no screening and three screening strategies: low-sensitivity gFOBT (performed annually), FIT (performed annually), and colonoscopy (performed every 10 years). These three tests are currently being used or considered for population-based screening of average-risk individuals in some Canadian provinces. They estimated the ICER for each strategy. The numerators were the differences in costs for each strategy relative to the preceding strategy (ranked in order of effectiveness), and the denominators were the differences in quality-adjusted life-years in hypothetical cohorts of 100,000 individuals undergoing screening. After adjustment for the utility and discount on future life-years, the mean numbers of discounted, quality-adjusted life-years were:

i. 15.20 with no screening
ii. 15.26 with low-sensitivity gFOBT annually
iii. 15.30 with FIT annually
iv. 15.32 with colonoscopy every 10 years

Whereas, the mean numbers of discounted, cost of screening for and treating CRC were:

i. CAN$783 with no screening
ii. CAN$1,415 with low-sensitivity gFOBT annually
iii. CAN$1,437 with FIT annually
iv. CAN$1,529 with colonoscopy every 10 years

Table 4: Result from the base-case analysis

Strategy	Mean cost, 2007 Can$†	Mean quality-adjusted life-years†	Incremental cost, 2007 Can$	Incremental quality-adjusted life-years	Incremental cost-effectiveness ratio‡
No screening	783	15.20	NA	NA	NA
Low-sensitivity guaiac fecal occult blood test, performed annually	1415	15.26	632	0.069	9159
Fecal immunochemical test, performed annually	1437	15.30	22	0.036	611
Colonoscopy, performed every 10 years	1529	15.32	92	0.015	6133

Note: NA = not applicable.
*The base case was 50-year-old individuals at average risk for colorectal cancer participating in one of the screening strategies or no screening.
†The average cost incurred and quality-adjusted life years realized by each individual.
‡Incremental cost effectiveness ratio = Incremental cost/Incremental quality-adjusted life years.

These three screening strategies were cost-effective in comparison with no screening, generated ICER of $9,159, $611, and $6,133 per quality-adjusted life year, respectively as shown in Table 4. The findings were robust to probabilistic sensitivity analysis. Based on analysis, the authors concluded that annual high-sensitivity faecal occult blood testing, such as a FIT or colonoscopy every 10 years offer the best value for the money in Canada. However, this study was subject to important limitations. The model did not incorporate the cost of establishing the infrastructure to implement population-based screening for CRC. The model was developed from the perspective of a third-party payer, such as a provincial ministry of health, the organization that decides on funding for a provincial screening programme for CRC. For this reason, lost productivity costs, which are necessary to determine the societal perspective, were not incorporated. Other important limitation were related to the authors findings which may be relevant only to those similar to their health care systems.[32]

An incremental cost-utility analysis using Markov model was performed by Heitman S *et al.* (2010) comparing the following CRC screening modalities: gFOBT annually, FIT annually, faecal DNA every three years, flexible sigmoidoscopy every five years, computed tomographic colonography (CTC) every five years, and colonoscopy every 10 years. These modalities were compared to each other and to a no screening among average-risk individuals, aged 50 to 75 years. For the baseline data of the model, they used adenoma and colorectal prevalence rates from a recent systematic review and based screening adherence, test performance, and colorectal treatment costs on available data. The outcome measures included lifetime costs, number of cancers, cancer-related deaths, quality-adjusted life-years gained, and incremental cost-utility ratios. Sensitivity and scenario analysis were performed. All costs are reported in 2008 CAN$. The study found that annual CRC screening using FIT, assuming mid-range test performance characteristics, was more effective and less costly compared to all strategies (including no screening). Using this screening modality (FIT-mid), among the lifetimes of 100,000 average-risk patients, it was postulated that number of cancers could be reduced from 4,857 to 1,393 (71.0%) and the number of CRC deaths from 1,782 to 457 (74.0%), while saving CAN$68 per person (Table 5). Although in the sensitivity and scenario analysis, screening patients using FIT became more expensive than a strategy of no screening when the test performance of FIT was reduced, or the cost of managing CRC was lowered, CRC screening with FIT remained the most economically attractive screening option. The authors concluded that this model-based economic analysis found FIT is more effective and less costly than all other colorectal screening strategies.

Furthermore, this study suggests that annual screening with FIT (assuming mid-range test performance characteristics) reduced the risk of CRC and CRC-related death, and lower health care costs in comparison to all other screening strategies and to no screening. Therefore, health policy makers should consider prioritizing funding for FIT as the screening modality for CRC.[33]

Table 5: Cancer outcomes and number of screening tests required during the lifetimes for a hypothetical 100,000 average risk patient cohort.

Screening Test	*n* Cancers Overall[a]	*n* Cancer Deaths	*n* Primary Screening Tests	*n* Colonoscopies	Cost Of Screening And Managing CRC (CAN$)
FIT-high	1,290	432	819,178	56,541	2,004
FIT-mid	1,393	457	822,077	53,909	1,833
CTC	1,796	593	188,315	58,354	2,409
Colonoscopy	1,825	624	155,210	N/A	2,100
Flex Sig	2,036	699	189,135	49,484	2,263
FIT-low	2,634	918	871,986	31,597	2,005
FDNA-5DT2	3,129	1,143	331,090	20,805	2,491
FOBT-low	3,457	1,250	889,168	21,805	2,195
FOBT-high	3,890	1,368	902,299	15,089	2,084
FDNA-5DT1	4,131	1,530	331,699	14,548	2,720
No screening	4,857	1,782	n/a	n/a	1,901

[a]*n* cancers overall include symptomatic and screen found CRC.
doi:10.1371/journal.pmed.1000370.t005

There was no retrievable evidence on the exact price or cost of the IFOBT fully automated analyzer. However, a population screening programme conducted in Italy (2004) reported that they spent €2,066 for three months on renting the analyzer.[20 level 3]

In the Malaysian context, the cost for qualitative IFOBT ranged from [redacted] to [redacted] per test. The most brand names used were VEDA LAB Hem Check-1 (France), ACON FOB One Step Faecal Occult Blood (USA), and Chemtrue One-Step FOBT Test (China) (email from Consultant Chemical Pathologist in Selayang Hospital, Selangor).

6.4 COMPETING TECHNOLOGIES

A recent prospective single-centre study was performed by Kalimutho M *et al.* (2011) to evaluate the sensitivity and specificity of faecal-based DNA (fDNA) versus IFOBT and calprotectin for CRC and adenoma detection. A total of 204 patients (age range 19 to 88 years) in Belfast, Northern Ireland, UK who came to gastroenterology unit to have a colonoscopy were recruited from December 2007 to August 2009 with symptoms such as abdominal pain or constipation.

They excluded patients with any of the following conditions: diarrhea due to insufficient faecal materials, familial adenomatous polyposis, hereditary non-polyposis CRC, and inflammatory bowel disease. Faeces were collected from the 204 subjects, fDNA analysis by PCR and DNA integrity assay (DIA) was quantified by quantitative-denaturing high performance liquid chromatography (QdHPLC). They performed four different gene amplifications for the DIA (APC, BRAF, KRAS, and p53) in order to determine the occurrence of L-DNA in faecal specimens. Calprotectin and IFOBT were assessed using Calprest ELISA kit and IFOBT test card (immunochromatographic sandwich assay principle), respectively. The diagnostic performance was calculated by ROC curve analysis, to determine the best cut-off value for the highest sensitivity and specificity of the assays. From the 192 faecal specimens analysed, 28 had CRC, 69 had adenoma, and 95 had CRC or polyp-free. Twenty-four of 28 CRC patients were identified using DIA in contrast with 14 of 27 using IFOBT (sensitivity of 86.0% versus 52.0% and a specificity of 81.0% versus 98.0%, respectively). For adenoma detection, the sensitivity of both methods turned out to be as low as 17.0% for DIA and 21.0% for IFOBT. To minimize false positive cases of the developed test (DIA), area under the curve of ROC was evaluated such that the sensitivity and specificity of average DIA (AVG-DIA) for cancer detection were 79.0% and 92.0%, respectively, and for IFOBT were 52.0% and 98.0%, respectively. The combination of DIA with IFOBT detects the majority of CRC cases with sensitivity of 89.0% and specificity of 95.0%, $p<0.001$. The combination also improved the sensitivity of polyps, particularly high-grade dysplasia and advance adenoma (33.0%, $p=0.0015$) as opposed to a single evaluation assay (17.0% to 21.0%), respectively. The study data suggested that the fDNA integrity assay by QdHPLC is a valid and feasible method with a high level of sensitivity in detecting individuals with CRC. Furthermore, the authors suggested a combination of QdHPLC-DIA, probably with APC-p53 together with IFOBT to enhance the detection rate of CRC and adenoma as a screening modality option.[34 level 3]

6.5 OTHER CONSIDERATIONS

6.5.1. Organizational

In Malaysia, currently there is no national CRC screening programme. However, there was an unpublished feasibility study on population based CRC screening in Malaysia, conducted by Noriah B *et al.* (2007) from Institute for Health Management. The aim of the study was to determine population's acceptance, barriers for screening from patient's perspective, the cost implication on the screening and to recommend suggestions for colorectal cancer screening.

A total of 605 respondents took part in this study through three approaches, namely house to house, awareness campaign and opportunistic testing in the District of Seremban, Negeri Sembilan from 15 September 2007 until 31 December 2007. A face to face interview using a validated questionnaire was carried out to obtain knowledge, attitude and practice of respondent in terms of CRC. All the respondents were given two types of FOBT kits for stool screening, that is Hemoccult SENSA (gFOBT) and Hemoccult ICT (IFOBT). Thirty percent of the test was done on SENSA and remaining 70.0% used the ICT. Respondents were given consent form prior to enrolment of the survey. Colonoscopy was arranged for those who were tested positive on FOBT screening and high risk respondent who has family history of colorectal cancer, personal history of Inflammatory Bowel Disease such as Crohn's Disease and Ulcerative Colitis. Results showed that the highest among the approach was house to house, followed by opportunistic testing and lastly awareness campaign. More than 90.0% of respondents returned the FOBT kits for testing. Out of 605 respondents, nine were found to be FOBT positive (1.5%) and referred for colonoscopy. Only six out of nine (66.7%) positive respondents underwent colonoscopy. The two respondents whom tested positive, one found to have colitis and another respondent had pedunculated with small sessile rectal polyps. The remaining four respondents yielded as no abnormality detected. Barriers for screening (FOBT) from patient's perspective were unsure to take the test, feeling well, no symptoms and they think that they understand about CRC. In terms of costing, the cheapest approach was awareness campaign followed by opportunistic testing and house to house being the most expensive. In conclusion, they indicated that it is feasible to conduct screening for early detection of CRC using FOBT because the acceptance rate was good and the respondents were enthusiastic even though the study was conducted during fasting month. The awareness campaign and opportunistic testing were the best approach and cost-effective, but again in Malaysian setting, all the three approaches are necessary depending on the area and ethnicity.[35]

The possibility that seasonal variations in temperature might influence the performance of IFOBT for CRC screening programme has not been described previously. One study which is the first to describe a relationship between the seasons and haemoglobin concentrations measured in faecal samples in a screening programme for CRC, showed a significant difference in the proportion of IFOBT positive results in the summer than in winter. A recent study has described the performance of the IFOBT was decreased (occurrence of false negative results) by a delay in time between faecal sampling and laboratory delivery because of haemoglobin degradation. If the instability of IFOBTs results in a seasonal variations in the screening positivity rate with increased false negative test rates during a hot weather like Malaysia, more effective ways need to be found to improve sample stability.

Until improved collection systems have been developed, screening programmes will need to consider methods which minimise the effect of seasonal variations in temperature on positive rates. Some of the mechanisms which might be adopted could include:

i. Requiring that samples be posted to the laboratory immediately after sample collection.

ii. Requiring that samples be stored prior to transportation to the laboratory in a domestic refrigerator.

iii. Insisting that participants record the sample collection date and then excluding those that fall outside a designated 'safe' period

iv. Improving the rapidity of transport between the participant and the testing laboratory

v. Refrigerating samples (perhaps using dedicated ice packs) during transport to the laboratory, a method used for faecal DNA testing.

vi. Testing immediately on receipt by the laboratory or refrigerating stored samples prior to analysis (freezing is known to interfere with some IFOBT systems).

vii. Adopting a more sensitive 'seasonal' strategy such as reducing the cut-off points from 100 ng/ml to 80 ng/ml or using a positive from either of two samples instead of a single sample during the summer or hot weather.

viii. Reducing the positivity cut-off of IFOBT for the whole programme to avoid the increase in false negative during the summer or hot weather, and accepting an increase in false positive during the winter.

All of the mechanisms describe above would have significant implications for a screening programme. Some would decrease programme participation, others would increase programme complexity and cost, and decrease efficiency.[25 level II-2, 26 level 3]

6.5.2. Ethical and legal consideration

Studies have shown that the more sensitive the test, the greater the detection rate and the greater the number of false results. This means that some people with cancer or a pre-malignant condition will be wrongly reassured and others will be subject to unnecessary procedures and stress. When cancers and adenomas have been missed, a negative result will give false reassurance, with the increased possibility that there will be delay in diagnosis and treatment.

The advantages of increased sensitivity have to be weighed against the significant increase in false positive, the consequential number of colonoscopies carried out, and the possible reduction in the specificity of the FOBT. False positive results expose healthy people to unnecessary intervention and alarm, as well as generating considerable additional costs. The credibility of a screening programme can easily be undermined if the screening tests are considered unreliable. In this review, false positive rates for IFOBT ranged from 1.5% to 6.0% for CRC.[16, 17, 20-23 level 3, 19, 24 level II-3, 36]

Now that studies have clarified the incidence of CRC and strategies that may be effective in detecting and treating it, there is concern about the potential response of insurance companies and employers. Some insurers already require women to state the date and result of their last cervical smear. If a CRC screening programme were introduced, applicants may also be required to supply the date and result of their last FOBT or colonoscopy, and be charged higher premiums if they have not been screened nor have a positive result. Other issues include whether a person could be refused cover on the basis of a screening test result or a refusal to have a test, and whether insurance companies would pay the cost of screening tests.[36]

In 1968, Wilson and Jungner authored a WHO document entitled “Principles and Practice of Screening for disease (Public Health Papers, No. 34)” has defined ten criteria to be met by mass screening programmes for it to be medically and ethically acceptable. This criterion has been reviewed in 2003 as in Appendix 5. Ethical analysis in this context weighs the probable or expected value of mass screening in the population concerned against the assumed or probable risks of adverse physical or psychological effects for those affected if mass screening is or is not done.

7.0 DISCUSSION

The diagnosis of CRC raises many questions and there is a need for clear, understandable answer. Therefore, the purpose of this HTA on IFOBT was to evaluate whether, and under what conditions, it would be effective, safe, and cost-effective tests for CRC screening among general population in Malaysia.

Overall, the studies that assessed the diagnostic accuracy or performance of IFOBT showed that it was effective for the detection of CRC and HRA. Positive predictive value ranged from 4.0% to 34.0% for CRC and from 11.2% to 40.3% for HRA. Sensitivity and specificity for CRC varied from 28.5% to 89.0% and from 86.4% to 97.0% respectively. False positive rate ranged from 1.5% to 6.0% for CRC.[16-18, 20-23, 25-26, 30]

The use of fully automated IFOBT assay would be highly desirable in a national population based screening programme because of the large number of tests to be done involving large number of laboratories. Automation allows time to be saved during development, better standardization of results, and the application of very strict quality control criteria. Because the test is quantitative, a concern about the optimal cut-off points or positivity threshold was raised. Many of the studies in the review indicated that from the viewpoint of diagnostic validity and cost-effectiveness, the recommended cut-off points varied from 100 ng/ml to 150 ng/ml. The sensitivity of IFOBT increased as the cut-off points decreased. The specificity of IFOBT increased as the cut-off points increased.[16-18, 20-23, 25-26, 30]

Although sensitivity of IFOBT for CRC or large adenomas has been reported, sensitivity to small adenomas was unknown. Previous reports indicated that gFOBT was not useful for identifying patients with small adenomas, and that this method detects small adenomas only by chance or serendipity.[37-39] One study showed that the IFOBT identified small adenomas (≤ 9 mm) with a level of sensitivity that was higher than the false positive rate (7.0% versus 4.5%, $p<0.001$).[23]

Haemoglobin is not stable in faeces; the globin component is degraded quite rapidly while the haem component is degraded more slowly by processes which include the removal of iron by colonic bacteria. The stability of globin in the wet collection systems used by most IFOBTs is less than that of the haem used in gFOBTs because globin is more susceptible to denaturation than haem. Moreover, the concentration of haemoglobin in IFOBT samples is very low, which increases its susceptibility to degradation. One study in the review which is the first to describe a relationship between the seasons and haemoglobin concentrations measured in faecal samples in a screening programme for CRC, showed a significant difference in the proportion of IFOBT positive results in the summer than in winter, a difference which is likely to be related to ambient temperature differences.[25] These results have important implications to the organization of IFOBT-based screening programmes in Malaysia since our temperature is much more higher compared to the temperature during winter. In a more recent study, van Rossum *et al.* described the performance of the IFOBT was decreased (occurrence of false negative results) by a delay in time between faecal sampling and laboratory delivery because of haemoglobin degradation.[26] Based on these finding, screening programme will need to consider methods which can minimise the effect of seasonal variations in temperature on positive rates such as sample collection, storage condition, sample analysis, and transportation.

The diagnostic accuracy of the FOBT for CRC was influenced by the number of faecal specimens, and collection on three consecutive days is the generally accepted method for the gFOBT.[6-8] However, for IFOBT, there is no clear understanding on the best number of faecal specimens to be collected in order to balance an appropriate screening test with optimal cost-effectiveness and high accuracy. The present economic analysis in the review suggests that a two-day faecal collection method is recommended for IFOBT screening from the aspects of cost-effectiveness, as well as diagnostic accuracy.[24]

The effectiveness of CRC screening programmes using gFOBT has been proven in three RCTs, one in USA and two in Europe (UK and Denmark). In these studies reduction in mortality ranged from 15.0% to 33.0% depending on the screening frequency (annual or biennial), the screening test sensitivity (unhydrated or rehydrated guaiac test), and the attendance rate.[6-8] As for IFOBT, there was no RCT to show the screening efficacy in reducing CRC mortality. However, there was a case-control study which showed a screening programme using IFOBT reduced the risk of CRC mortality from 23.0% to 60.0%.[27] Another case-control study also revealed that a screening programme with IFOBT can be effective for prevention of advanced CRC (risk of developing advanced CRC was reduced by 28.0% to 46.0%).[29] One study reported that regular IFOBT can detect precancerous lesions and CRC in early stages and thus reduce mortality from CRC.[28]

From the viewpoint of cost-effectiveness, two studies evaluated the optimum cut-off points of faecal haemoglobin whereas one evaluated the optimum number of faecal specimen to collect for use in IFOBT as a means of screening for CRC.[18-19,24] In 2010, a cost-effectiveness study demonstrated that the most three screening strategies in Canada (low-sensitivity gFOBT performed annually, FIT performed annually, and colonoscopy performed every 10 years) were cost-effective in comparison with no screening, generated ICER of $9,159, $611, and $6,133 per quality-adjusted life year, respectively.[32] An incremental cost-utility analysis using Markov model revealed that CRC screening using FIT, assuming mid-range test performance characteristic, was more effective and less costly compare to all strategies (including no screening). Using this screening modality (FIT-mid), among the lifetimes of 100,000 average-risk patients, it was postulated that the number of cancer could be reduced to about 71.0% and the number of CRC deaths to about 74.0%, while saving CAN$68 per person.[33] In the Malaysian context, the cost for qualitative IFOBT ranged from [redacted] to [redacted] per test.

Faecal DNA testing is a recently developed technique for CRC screening, which is based on faecal DNA analysis of cells that have been exfoliated from colorectal polyps and cancers. Differences in sensitivity between IFOBTs and faecal DNA testing have not been compare in any prospective study, but a recent study showed sensitivity with DNA testing to be 86.0% for cancer and 17.0% for advanced adenoma. In term of cost, the faecal DNA tests are more expensive than IFOBTs and currently lack supporting clinical data from large population screening studies.[34] The USPSTF also concluded that the evidence is insufficient to assess the benefits and harm of faecal DNA testing as screening modalities for CRC.[4]

Limitations

This review has several limitations. Although there was no restriction in language during the search but only English full text articles were included in the report. Although every effort has been made to retrieve full text articles, there were eight abstracts which the authors failed to retrieve full text. Most of the articles meeting inclusion criteria for this review were observational studies and that there were no RCTs evaluating diagnostic performance. Most of the diagnostic accuracy studies on IFOBT may have introduced bias and limited the conclusions. These limitations included possible verification bias in studies where only those with a positive IFOBT results follow-up by colonoscopy with biopsy, which is the reference or gold standard test while patients with negative IFOBT results were verified with clinical follow-up because of the invasiveness of colonoscopy procedure. Because of this, many studies reported only the PPV of CRC screening.

8.0 CONCLUSION

8.1 Diagnostic accuracy and effectiveness

There was fair level of evidence to suggest that:-

a. The sensitivity and specificity of IFOBT varies with the cut-off points or positivity threshold of haemoglobin. The sensitivity of IFOBT (cut-off point between 100 ng/ml to 150 ng/ml) is around 89.0% for CRC whereas specificity around 97.0%. Positive predictive value (PPV) ranged from 4.0% to 34.0% for CRC and from 11.2% to 40.3% for HRA. False positive rate ranged from 1.5% to 6.0% for CRC.

b. Immunochemical faecal occult blood test (IFOBT) identified small adenomas (≤ 9 mm) with a level of sensitivity that was higher than the false positive rate (7.0% versus 4.5%, $p<0.001$).

c. A significant difference in the proportion of IFOBT positive results in the summer than in winter as there was a significant fall in haemoglobin concentration at higher ambient temperatures.

d. The performance of the IFOBT was decreased (occurrence of false negative results) by a delay in time between faecal sampling and laboratory delivery because of haemoglobin degradation.

e. A two-day faecal collection method was found to be more cost-effective compared to three-day faecal collection method.

f. A screening programme using IFOBT reduced the risk of CRC mortality by 23.0% to 60.0%.

g. A screening programme using IFOBT can be effective for prevention of advanced CRC by 28.0% to 46.0%.and thus reduce mortality from CRC

h. Regular IFOBT can detect precancerous lesions and CRC in early stages.

8.2 Safety

There was no retrievable evidence on the safety of IFOBT for CRC screening. However, several test methods on IFOBT have US FDA approval.

8.3 Cost/cost-effectiveness/economic evaluation

There was evidence to suggest that:-

a. Faecal immunochemical test (FIT) was cost-effective in comparison with no screening. The generated ICERs were USD$905 and CAN$611 per quality-adjusted life year in Taiwan and Canada, respectively.

b. Annual FIT with mid-range testing characteristics, was more effective and less costly compared to all strategies (including no screening). By using this modality, it was postulated that the number of CRC could be reduced to about 71.0% and the numbers of CRC deaths to about 74.0%, while saving CAN$68 per person.

8.4. Competing technologies

There was insufficient evidence to assess the benefits and harm of faecal DNA testing as screening modalities for CRC.

8.5. Other considerations:

i. The barriers for screening may be different in different countries because of the different health-care system structure and cultural acceptance.

ii. The introduction of automated testing technology could reduce the number of staff required to perform analysis. However, the staff with the skills required to use the automated equipment are likely to prove more expensive.

iii. Proper training of staff involved in the screening programme is essential since IFOBT require experience as well as continuous training.

iv. For a mass screening programme to be medically and ethically acceptable, the WHO criteria for mass screening programmes as shown in Appendix 5 have to be met.

v. Screening programme will need to consider methods which can minimise the effect of seasonal variations in temperature on positive rates such as sample collection, transportation, storage condition, and sample analysis.

9.0 RECOMMENDATION

Based on the above review, IFOBT can be used in Malaysia as a screening test for CRC. The use of fully automated IFOBT assay would be highly desirable should a screening programme is to be introduced because of the large number of tests to be done and involving large number of laboratories. Automation allows time to be saved and could reduce the number of staff required to perform analysis, better standardization of results, and the application of very strict quality control criteria. However, one has to take cognizance of the staff with the skills required to use the automated equipment that they must be well trained.

From the viewpoint of diagnostic validity and cost-effectiveness, the recommended cut-off points varied from 100 ng/ml to 150 ng/ml.
A two-day faecal collection method was found to be more cost-effective compared to three-day faecal collection method for use in IFOBT as a means of screening for CRC.

However, organizational issues such as training, manpower, good referral centre or system, and funding as well as sample collection, storage condition, sample analysis, and transportation need to be addressed at all levels. One must recognized methods to minimise the effect of high temperature and lag time before the faecal sample can be analyzed.

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11.0 APPENDICIES

Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2

HIERARCHY OF EVIDENCE FOR TEST ACCURACY STUDIES

Level	Description	
1.	A blind comparison with reference standard among an appropriate sample of consecutive patients	
2.	Any one of the following	Narrow population spectrum
3.	Any two of the following	Differential use of reference standard
4.	Any three or more of the following	Reference standard not blind Case control study
5.	Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.	

SOURCE: NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition)

Appendix 3

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL IMMUNOCHEMICAL FAECAL OCCULT BLOOD TEST (IFOBT) FOR COLORECTAL CANCER (CRC) SCREENING

1.0 BACKGROUND INFORMATION

Colorectal cancer (CRC) is one of the most common forms of gastrointestinal (GI) cancer in the world today. It is the fourth most common form of cancer worldwide and the most frequent in North America, Australia, New Zealand, Argentina, and parts of Europe.[1] In the United States, it is the third most common cancer diagnosed in both men and women; and for 2010, the estimated number of new cases of colon cancer and rectal cancer were 102,900 and 39,670, respectively.[2] According to the latest report of the National Cancer Registry (NCR) in Peninsular Malaysia 2006, CRC was the second most common cancer after breast cancer. It is the first among male and also second among female. A total of 2,866 cases were registered with NCR in 2006 and it represented 13.2% of all cases registered. The incidence of CRC in Peninsular Malaysia increased with age with the overall age-standardised incidence (ASR) of 18.4 per 100,000 populations. The incidence was slightly higher among males (ASR of 21.6 per 100.000) compared to females (ASR of 15.4 per 100,000). The incidence was highest among Chinese where the ASR was 21.4 per 100,000 and were lower in Indian and Malay where the ASR was 11.3 per 100,000 and 9.5 per 100,000 respectively.[3]

The diagnosis of CRC raises many questions and there is a need for clear, understandable answer. People with CRC may develop a number of non-specific signs and symptoms. These include a change in bowel habits such as diarrhoea, constipation or a feeling that the bowel does not empty completely, and stools with bright red or very dark blood. They may also experience abdominal pain, including frequent bloating, fullness and cramps. Stools may appear thinner. They may also be constantly tired and anaemic, or experience an unexplained loss of weight and appetite. However, most of these symptoms may also to be caused by conditions other than CRC, such as infection, hemorrhoids, or inflammatory bowel disease.[4]

The stage of CRC describes the extent of the cancer in the body and one of the most important factor in determining prognosis and treatment options. It is based on how far the cancer has grown into the wall of intestine, whether or not it has reached nearby structures, and whether or not it has spread to the lymph nodes or distant organs. Listed below are discriptions of the various stages of CRC based on Malaysian Oncological Society:[4]

Stage I : Cancer is confined to the inner lining of the colon or rectum

Stage II : Cancer spreads through the wall of the colon or rectum

Stage III : Cancer spreads to nearby lymph nodes

Stage IV : Cancer spreads to distant parts of the body, such as the liver or lungs

Several major organizations, including the U.S. Preventive Services Task Force (a group of experts convened by the U.S. Public Health Service), the American Cancer Society, and professional societies, have developed guidelines for colorectal cancer screening. Although some details of their recommendations vary regarding which screening tests to use and how often to be screened, all of these organizations support screening for colorectal cancer.[5] It is important that a screening test, which is directed at healthy people, have an impact measurable at the population level. People are inherently reluctant to undergo invasive and inconvenient tests for screening such as colonoscopy without strong motivation.[6]

There was evidence to show screening for CRC will reduce CRC mortality[7-11] and the only contentious issue is which screening test to use. There are several different tests that can be used to screen for CRC. The test can be divided into two broad groups:[2]

i. **Tests that can find both colorectal polyps and cancer:**
These test look at the structure of the colon itself to find any abnormal areas. This is done either with a scope inserted into the rectum or with special imaging (x-ray) tests. Polyps found before they become cancerous can be removed, so these tests may prevent CRC. This includes flexible sigmoidoscopy, colonoscopy, double-contrast barium enema (DCBE), CT colonography (virtual colonoscopy), and digital rectal examination (DRE). However, this tests are invasive and may not be acceptable as a primary screening tools in asymptomatic individuals.

ii. **Tests that mainly find cancer:**
These involve testing the stool (faeces) for sign of occult/hidden blood that may be present. These tests are less invasive and easier to be conducted such as faecal occult blood test (FOBT), immunochemical faecal occult blood test (IFOBT) which is known as faecal immunochemical test (FIT), and stool DNA test. The rational of using this technology as a screening test is based on the concept that blood vessels at the surface of larger colorectal polyps or cancers are often fragile and easily damaged by the passage of faeces and will bleed, and therefore become detectable.

Technical Features

The main commercial FOBT technologies detect either of two classes of hemoglobin product in faeces: [2, 12]

i. **FOBT use a chemical reaction; the guaiac-based (gFOBT)**
Test involves smearing some feaces on to some absorbent paper that has been treated with a chemical. Hydrogen peroxide is then dropped on to the paper; if trace amounts of blood are present, the paper will change color in one or two seconds. This method works as the heme component in hemoglobin has a peroxidase-like effect, rapidly breaking down hydrogen peroxide. By far the best evaluated type are the readily available Hemoccult tests (Hemoccult II and Hemoccult SENSA).

ii. **IFOBT or FIT; use antibodies specific for human haemoglobin**
This test reacts to part of the human haemoglobin protein, which is found on red blood cells. The IFOBT is done essentially the same way as the FOBT, but some people may find it easier to use because there are no drug or dietary restrictions (vitamins or foods do not affect the IFOBT) and sample collection may take less effort. This test is also less likely to react to bleeding from parts of the upper digestive tract, such as the stomach. Example include HemeSelect, HemSP, Detectacol, Hemoccult ICT, InSure and Hemolex. Availability of these varies greatly.

The IFOBT, like the FOBT, may not detect a tumour that is not bleeding, so multiple stool samples should be tested. And if the results are positive for hidden blood, a colonoscopy is required to investigate further. In order to be beneficial the test must be repeated every year.[2] For screening in Malaysia, healthy people aged between 40 and 45 years may undergo an annual FOBT, flexible sigmoidoscopy every five years and colonoscopy every 10 years. People with more risk factors may start screening earlier.[4]

Alternative Screening Tools

Virtual colonoscopy, despite improvements in technology, continues to show widely varying results with sensitivities for detecting polyps ≥ 10 mm ranging from 55% to 92%. As such it is still not ready for population screening. Faecal calprotectin failed to live up to its initial promise in subsequent studies. Faecal DNA test are affected by the relatively low frequency of single marker alterations in CRC. Even the use of a broad panel of markers in faecal DNA still fails to be convincing for population screening.[1] Scientists are still studying CRC screening methods, both alone and in combination, to determine how effective they are. Studies are also under way to clarify the potential risks, or harms, of each test.[5]

This HTA was requested by Gastroenterologist and Physician in Hospital Sultanah Bahiyah, Alor Star, Kedah, to look into the suitability of using IFOBT for CRC screening in Malaysia.

2.0 POLICY QUESTION

2.1 Should IFOBT be used as a screening test for colorectal cancer in Malaysia?

2.2 Which IFOBT is the most suitable to be used for CRC screening in Malaysia?

3.0 OBJECTIVE

3.1 To determine the diagnostic accuracy various type of IFOBT for CRC screening among general population.

3.2 To determine the benefits of CRC screening using various type of IFOBT compared with no screening, or screening using stool DNA test with regards to patient outcomes such as detection rate, mortality rate, quality of life and quality adjusted life years gained.

3.3 To look into safety of using various type of IFOBT as a screening test for CRC.

3.4 To determine the economic impacts using various type of IFOBT for CRC screening among general population.

3.5 To look into the ethical, legal, and organizational aspects related to CRC screening using various type of IFOBT.

4.0 METHODOLOGY

4.1. Search Strategy

Electronic database will be searched for published literatures pertaining to IFOBT for CRC screening.

4.1.1 Databases as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the bibliographies of the related articles.

4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.

4.1.4 There will be no limitation applied in the search such as year and language.

4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

a. Study design : Cross-sectional diagnostic accuracy studies, HTA reports, systematic review, randomized controlled trial (RCT), cohort, case-control, and economic evaluation studies.

b. Population : Adults

c. Intervention : Various type of IFOBT

d. Comparators : i) No comparator

ii) Stool DNA test

e. Outcome :

i. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IFOBT.

ii. Detection rate, mortality rate, quality of life, quality adjusted life years (QALY) gained.

iii. Adverse events related to the use of IFOBT as a CRC screening test.

iv. Cost, cost-benefit, cost-effectiveness, and cost utility of using IFOBT for CRC screening.

4.2.2 Exclusion criteria

i. Animal study
ii. Narrative review
iii. Laboratory study

Based on the above inclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Data extraction strategy

The following data will be extracted:

4.3.1 Details of methods and study population characteristics.

4.3.2 Detail of intervention and comparators.

4.3.3 Details of individual outcomes for effectiveness, safety and cost associated with IFOBT for CRC screening.

4.3.4 Details on diagnostic accuracy (sensitivity, specificity, PPV, NPV) of screening tests used in CRC screening.

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4 Quality assessment strategy

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP).

4.5 Methods of analysis/synthesis

Data on the diagnostic accuracy, effectiveness, safety and cost-effectiveness of IFOBT for CRC screening will be presented in tabulated format with narrative summaries. No meta-analysis will be conducted for this Health Technology Assessment.

5.0 Report writing

Appendix 4

Search strategy

1. MEDLINE (OVID) 1950 to June week 1 2011

01. Bowel cancer.tw.
02. CRC.tw.
03. (((colorectal or colon or colonic or sigmoid or rectal or rectum or anus or anal or bowel) adj3 neoplasm$) or cancer$ or carcinoma$ or tumo?r$).tw.
04. colorectal neoplasms/ or colonic neoplasms/ or sigmoid neoplasms/ or rectal neoplasms/ or anus neoplasms/
05. 1 or 2 or 3 or 4
06. Immunologic Tests/ or Immunochemistry/
07. f?ecal immunochemical test$.tw.
08. (Immunochemical adj (f?ecal occult blood test$ or faeces test$ or stool test$ or FOBT$1)).tw.
09. (immunologic$ adj (f?ecal occult blood test$ or FOB test$ or FOB$1 or test$)).tw.
10. (IFOBT$1 or I-FOBT$1 or auto iFOBT or qFIT or LA-FOBT or Quantitative iFOBT's or Hemosure IFOBT or CFOBT or SFOBT).tw.
11. (automatic immunochemical f?ecal occult blood test$ or automated immunochemical FOBT or immune f?ecal occult blood test$).tw.
12. or/6-11
13. (F?ecal DNA test$ or F?ecal DNA or fluorescence long DNA test$ or FL-DNA test Stool-based deoxyribonucleic acid test$ or L-DNA).tw.
14. 5 and 12 and 13
15. 5 and 12
16. limit 15 to "diagnosis (best balance of sensitivity and specificity)"

2. EBM Reviews:

Cochrane Database of Systematic Reviews (2005 to May 2011), Cochrane Central Register of Controlled Trials (2nd Quarter 2011), HTA Databases (2nd Quarter 2011), Cochrane Methodology Register (2nd Quarter 2011), ACP Journal Club (1991 to May 2011), NHS Economic Evaluation Database (2nd Quarter 2011) via OVID

01. Bowel cancer.tw.
02. CRC.tw.

03. (((colorectal or colon or colonic or sigmoid or rectal or rectum or anus or anal or bowel) adj3 neoplasm$) or cancer$ or carcinoma$ or tumo?r$).tw.
04. colorectal neoplasms/ or colonic neoplasms/ or sigmoid neoplasms/ or rectal neoplasms/ or anus neoplasms/
05. 1 or 2 or 3 or 4
06. Immunologic Tests/ or Immunochemistry/
07. f?ecal immunochemical test$.tw.
08. (Immunochemical adj (f?ecal occult blood test$ or faeces test$ or stool test$ or FOBT$1)).tw.
09. (immunologic$ adj (f?ecal occult blood test$ or FOB test$ or FOB$1 or test$)).tw.
10. (IFOBT$1 or I-FOBT$1 or auto iFOBT or qFIT or LA-FOBT or Quantitative iFOBT's or Hemosure IFOBT or CFOBT or SFOBT).tw.
11. (automatic immunochemical f?ecal occult blood test$ or automated immunochemical FOBT or immune f?ecal occult blood test$).tw.
12. or/6-11
13. (F?ecal DNA test$ or F?ecal DNA or fluorescence long DNA test$ or FL-DNA test Stool-based deoxyribonucleic acid test$ or L-DNA).tw.
14. 5 and 12 and 13
15. 5 and 12
16. limit 15 to "diagnosis (best balance of sensitivity and specificity)"

3. PubMed

MESH	TEXT WORD
Colorectal Neoplasms Colonic Neoplasms Sigmoid Neoplasms Rectal Neoplasms Anus Neoplasms	(colorectal tumor* OR colorectal neoplasm* OR colorectal carcinoma* OR colorectal cancer * OR colonic neoplasm OR colon neoplasm* OR colon cancer* OR sigmoid neoplasm*) sigmoid cancer* OR sigmoid colon neoplasm* OR sigmoidal cancer* OR sigmoid colon cancer* rectal neoplasm* OR rectum neoplasm* OR rectal tumor OR rectal cancer* OR rectum cancer* anal neoplasm OR anus neoplasm OR anal Cancer OR anus cancer
	Immunochemical fecal occult blood test * OR Immunochemical FOBT OR immunochemical stool test* OR faecal immunochemical test* Immunologic* faecal occult blood test * OR Immunologic* FOB test Immunologic*$ FOB1 OR Immunologic* test* latex agglutination immunochemical faecal occult blood test* IFOBT OR I-FOBT OR auto iFOBT OR qFIT OR LA-FOBT or Quantitative iFOBT's OR Hemosure IFOBT OR CFOBT OR SFOBT automatic immunochemical faecal occult blood test* OR automated immunochemical FOBT OR immune faecal occult blood test*

Appendix 5

Screening criteria

The Wilson-Jungner criteria for appraising the validity of a screening programme

1. The condition being screened for should be an important health problem
2. The natural history of the condition should be well understood
3. There should be a detectable early stage
4. Treatment at an early stage should be of more benefit than at a later stage
5. A suitable test should be devised for the early stage
6. The test should be acceptable
7. Intervals for repeating the test should be determined
8. Adequate health service provision should be made for the extra clinical workload resulting from screening
9. The risks, both physical and psychological, should be less than the benefits
10. The costs should be balanced against the benefits

World Health Organisation 1968

Criteria for appraising the viability, effectiveness and appropriateness of a screening programme 2003

The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested for, should be clearly set out.

The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme.

The screening programme

13. There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (for example, Down's syndrome and cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially. and ethically acceptable to health professionals and the public.
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money).
17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

18. Adequate staffing and facilities for testing, diagnosis, treatment, and programme management should be available prior to the commencement of the screening programme.

19. All other options for managing the condition should have been considered (for example, improving treatment and providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.

20. Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

22. If screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members.

http://www.gp-training.net/training/tutorials/management/audit/screen.htm

APPENDIX 6

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	1. Castiglione G, Zappa M, Grazzini G *et al.* Screening for colorectal cancer by faecal occult blood test: comparison of immunochemical tests. J Med Screen. 2000; 7: 35-37
Study type and Methods	Cross-sectional study The aim of the study was to compare the performance of two IFOBT in a population based screening programme in Florence, Italy. Both tests were evaluated by a single determination. Reversed passive haemagglutination (RPHA) (Immudia Hem-Sp or Hemeselect) and latex agglutination (Hdia) (OC-Hemodia), the latter being evaluated according to different positivity thresholds. Positivity rates, the prevalence of screen positive cancer in the population, and PPVs for CRC or for high risk adenomas, were calculated and compared between 2 tests.
LE	3
Num. of pts and Pt characteristics	5,884 subjects (2,997 women, mean age 59.6; 2,867 men, mean age 59.5) were recruited every 2 year. Subjects were asked to collect faeces samples using RPHA cards and Hdia sticks on a single bowel movement and return kits as soon as possible after faeces collection.
Intervention	IFOBT used: 1. Hdia (OC-Hemodia) interpreted according to three positivity thresholds (ng/ml) i. 100 (Hdia100) ii. 150 (Hdia150) iii. 200 (Hdia200) 2. RPHA (Immudia Hem-Sp, FujiRebio, Tokyo or Hemeselect, SmithKline Diagnostics, Palo Alto)
Comparison	Pancolonoscopy or a combination of partial colonoscopy and double contrast barium enema when pancolonoscopy is impossible (Subjects with positive IFOBT results).
Follow up	Between December 1996 and October 1998
Outcome measures	**Positivity rates** were 3.3% for RPHA, 3.5% for Hdia100, 2.5% for Hdia150, 2.0% for Hdia200. Among subjects complying with the diagnostic work up, **CRC was detected in 19 subjects** (17 in RPHA, 16 in Hdia100, 15 in Hdia150, 14 in Hdia200) and **high risk adenoma/s in 41 subjects** (28 in RPHA, 32 in Hdia100, 29 in Hdia150, 25 in Hdia200). **The prevalence of screen positive CRC** in the population was 2.9‰ for RPHA, 2.7‰ for Hdia100, 2.6‰ for Hdia150, 2.4‰ for Hdia200. **The prevalence of screen positive high risk adenomas** in the population was 4.8‰ for RPHA, 5.4‰ for Hdia100, 4.9‰ for Hdia150, 4.2‰ for Hdia200. No significant difference between tests was found for the **PPVs** for CRC or adenomas. **Authors conclusion:** Hdia100 was as sensitive as RPHA for cancer and high risk adenomas. As Hdia is less technically complex than RPHA, it is a valid alternative to the latter, provided that full automation of the development procedure is available. Increasing the positivity threshold of Hdia up to 150 or 200 ng of haemoglobin/mg of specimen solution is not advisable as the increase in specificity is too small to justify the corresponding decrease in the detection of screen positive cancers in the population.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	2. Castiglione G, Grazzini G, Miccinesi G *et al.* Basic variables at different positivity thresholds of a quantitative immunochemical test for faecal occult blood. J Med Screen. 2002; 9: 99-103
Study type and Methods	Cross-sectional study The aim of this study was to interpret the overall experience with latex agglutination test (LAT) according to different positivity thresholds. A population based screening programme is currently running involving subjects aged 50-70, invited every 2 years to have an FOBT in Florence, Italy. LAT is the standard screening test and has a positivity threshold for further diagnostic tests of 100 ng haemoglobin/ml of sample solution. In their preliminary study and the current study, only tests with concentration of 100 ng haemoglobin/ml sample solution or higher were considered positive. The positivity rates, detection rates for CRC, high risk adenomas, or low risk adenomas, and PPVs for CRC, high risk adenomas, and low risk adenomas were calculated for each positivity threshold and were then compared.
LE	3
Num. of pts and Pt characteristics	A total of 11,774 subjects attended screening for the first time (6,063 women, mean age 59.1 years; 5,711 men, mean age 59.2 years). 7,358 at subsequent screening (3,746 women, mean age 60.5 years; 3,612 men, mean age 60.8 years).
Intervention	IFOBT used: LAT (OC-Hemodia, Eiken, Tokyo, Japan). Assays were performed in laboratory by a completely automated procedure using equipment provided by the manufacturer (OC-Sensor, Eiken, Tokyo, Japan). Positivity rates were calculated with positivity thresholds put at every 25 ng haemoglobin/ml sample solution (LAT25, LAT50, LAT75, and LAT100). Performance of the test were interpreted with 11 positivity thresholds put at every 10 ng/ml interval between 100 and 200 ng/ml (LAT100, LAT110, LAT120, ...LAT200).
Comparison	Colonoscopy or a combination of partial colonoscopy and double contrast barium enema. (Subjects with positive IFOBT results).
Follow up	From December 1996 to December 2001
Outcome measures	Progressively increasing the positivity threshold from 100 to 200 ng/ml showed: (a) **A decrease in positivity rates** from 4.2% to 2.4% and from 3.4% to 1.6% in first and subsequent screening, respectively. (b)**A decrease in detection rates** for CRC (3.3‰ to 2.7‰) or high risk adenomas (7.9‰ to 5.9‰) in first screening; and 1.6‰ to 1.4‰ for CRC, or 4.9‰ to 2.3‰ for high risk adenomas in subsequent screening. (c) **An increase in PPVs** for **cancer** from 9.0% to 13.4% and from 5.5% to 10.9% in first and subsequent screening, respectively. (d) **An increase in PPVs** for **high risk adenomas** from 21.3% to 28.9% and from 16.6% to 18.5% in first and subsequent screening, respectively. **Authors conclusion:** Increasing the positivity threshold of the LAT reduces recall rate and improve PPV for cancer or high risk adenomas but substantially decreases the detection rate of CRC and high risk adenomas. For this reason increasing the positivity cut off for LATs is not advisable. On the other hand decreasing the positivity threshold would increase recall rate and sensitivity of screening.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	3. Nakama H, Zhang B, and Zhang X. Evaluation of the optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer. European Journal of Cancer. 2001; 37: 398-401
Study type and Methods	Cost-effectiveness and diagnostic validity These study was carried out to assess the optimum cut-off point for IFOBT (OC-Hemodia) using a 2-day method as a means of screening for CRC. The costs of IFOBT as well as colonoscopy procedure were calculated. The average cost to detect 1 patient with CRC, and the sensitivity and specificity of these 3 cut-off point of fecal haemoglobin were evaluated.
LE	II-3
Num. of pts and Pt characteristics	4,260 asymptomatic people aged over 40 years, gave samples for IFOBT and colonoscopy was carried out during a medical check-up.
Intervention	IFOBT used: OC-Hemodia with three cut-off levels of fecal haemoglobin were used: 50, 150, and 300 ng/ml.
Comparison	Colonoscopy (all subjects)
Follow up	Between April 1990 and March 1999
Outcome measures	A total of **27 patients with CRC** were diagnosed by colonoscopy. **Positive cases of an IFOBT** were 278 (6.5%), 175 (4.1%), and 139 (3.3%) using the 50, 150, and 300 ng/ml cut-off levels. The numbers of patients with CRC detected by colonoscopic examination were 24, 22 and 15 using the 50, 150, and 300 ng/ml cut-off levels. Accordingly, the **sensitivity** and **specificity** were calculated as: 24/27 (89%) and 3,979/4,233 (94%) for the 50 ng/ml level 22/27 (81%) and 4,080/4,233 (96%) for the 150 ng/ml level, 15/27 (56%) and 4,109/4,233 (97%) for the 300 ng/ml level Thus, there were significant differences in the sensitivity between the 50 and 300 ng/ml levels ($P < 0.05$) as well as between the 150 and 300 ng/ml levels ($P < 0.05$), and a significant differences in the specificity between the 50 and 300 ng/ml levels ($P < 0.05$). However, no significant difference was observed in the specificity between the 50 and 150 ng/ml levels. The findings indicated that the cut-off point of **150 ng/ml** fecal haemoglobin is recommended for IFOBT by OC-Hemodia, from the viewpoints of cost-effectiveness, as well as diagnostic validity.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	4. Li SC, Chao SL, Shu HC *et al.* Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16). Journal of Medical Screening. 2007; 14: 191-199
Study type and Methods	Cost-effectiveness analysis The optimal cut-off point of IFOBT applied to a Taiwan population-based screening for CRC was determined by **receiver operating characteristics (ROC) curve analysis** and further assessed by cost-effectiveness analysis (Markov decision model and Markov cohort simulation). Data from screen-detected cases were collected for the cut-off above 100 ng/ml and obtained interval cancer from a nationwide cancer registry for a cut-off below 100 ng/ml. Economic evaluation was further applied to identifying the optimal cut-off by assessing the minimum incremental cost-effectiveness ratio (ICER), an indicator for cost per life year gained (effectiveness), given a series of cut-offs of IFOBT, ranging from 30 to 200 ng/ml compared with no screening.
LE	II-3
Num. of pts and Pt characteristics	A total of 56,968 subjects (including 21,502 men and 35,466 women) were enrolled in the KCIS screening programme (data used for producing ROC curve analysis). Out of 56,968 subjects, 22,672 subjects aged 50 years or older were invited annually to have an uptake of IFOBT (58% were woman). The mean age was 63.36 ± 9.20 years. The model had a hypothetical cohort from people aged 50-80 years with population size and the make-up of demographic characteristic identical to subjects in the KCIS programme.
Intervention	1-day IFOBT method with a brush-type sampler was given to each eligible subject The stool sample was uploaded to the automated machine to yield a series of quantitative readings of IFOBT value.
Comparison	Colonoscopy (Subjects with positive IFOBT results).
Follow up	
Outcome measures	**ROC curve analysis** The area under curve was **0.87** (95% CI: 0.81-0.93). The **optimal cut-off** was **100 ng/ml** at which the corresponding sensitivity, false-positive and odds of being affected given a positive result (OAPR) for detection of CRC were **81.5%** (95% CI: 70.2-89.2), **5.7%** (95% CI: 5.4-6.0), and **1.24** (95% CI: 1.19-1.32), respectively. **Authors conclusion:** They used cost-effectiveness to identify 110 ng/ml as the optimal cut-off of IFOBT in a Taiwanese population-based screening for CRC. Their model provides a useful approach for health policy-makers in designing population-based screening for CRC to determine the optimal cut-off of IFOBT when cost and effectiveness need to be taken into account.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	5. Crotta S, Castiglione G, Grazzini G *et al.* Feasibility study of colorectal cancer screening by immunochemical faecal occult blood testing: results in a northern Italian community. European Journal of Gastroenterology & Hepatology. 2004; 16: 33-37
Study type and Methods	Cross-sectional study A pilot study in two municipalities of the region Valle d'Aosta, Italy was performed, with the aim of evaluating the feasibility of a regional screening programme for CRC by latex IFOBT. Attendance rates were calculated by sex, age, residence, distribution modalities and reference GP. In addition, positivity rates and detection rates for CRC, adenomas and high-risk adenomas were calculated.
LE	3
Num. of pts and Pt characteristics	A total of 2,961 subjects (1,403 males, 1,558 females) aged 50-74 years were invited by mail to perform a one-day IFOBT without any dietary restrictions and with a positive treshold put at 100 ng/ml.
Intervention	The IFOBT used was that based on latex agglutination (OC-Hemodia, Eiken, Tokyo, Japan). Returned specimens were processed by means of a completely automated procedure using the equipment provided by the manufacturer (OC Sensor, Eiken, Tokyo, Japan).
Comparison	Colonoscopy and double contrast barium enema if colonoscopy was incomplete (Subjects with positive IFOBT results).
Follow up	September to December 2001
Outcome measures	A total of **1,631 subjects** (710 males, mean age 59.3 years; 921 females, mean age 61.7 years) performed the screening test, with an **overall compliance of 55.1%.** **72 (4.4%)** subjects had a **positive FOBT**. **67 (93.1%)** agreed to undergo **colonoscopy**. **Detection rates** for cancer and adenomas were 1.8 per 1,000 and 16.6 per 1,000, respectively. **PPVs** for cancer and adenomas were 4.5% and 40.3%, respectively. **Authors conclusion:** Screening had an adequate attendance rate and the majority of the indicators were satisfactory. The use of a one-day quantitative latex FOBT with no dietary restriction, automation of the analytical procedure, and a positive threshold of 100 ng/ml has shown that a programme based on this test is feasible in both organizational and attendance terms. On the basis of this experience, the extension of the screening on a regional basis is suggested.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	6. Fenocchi E, Martinez L, Tolve J *et al.* Screening for colorectal cancer in Uruguay with an immunochemical faecal occult blood test. European Journal of Cancer Prevention. 2006; 15: 384-390
Study type and Methods	Cross-sectional study The aim of this study was to evaluate the feasibility of CRC screening with an IFOBT with no dietary restrictions in an average-risk population in Uruguay. The study developed according to the following stages: Stage 1: recruitment Stage 2: interview Stage 3: distribution of test and reception of samples Stage 4: IFOBT analysis Stage 5: colon video-endoscopy Stage 6: pathology Stage 7: analysis of the results Areas of evaluation include compliance with IFOBT and colonoscopy, the positivity rate and the PPV of IFOBT and the detection rates for CRC and high-risk adenoma.
LE	3
Num. of pts and Pt characteristics	11,734 (3,663 men, mean age 61.3 ± 9.6 years; 8,071 women, mean age 61.2 ± 9.1 years) volunteers were enrolled in the CRC screening programme
Intervention	IFOBT kit (OC-Hemodia, Eiken, Tokyo, Japan) to be used at home on a single day. An automated system (OC-Sensor II, Eiken, Tokyo, Japan) was used for processing the samples with a cut-off haemoglobin level of 100 ng/ml.
Comparison	Videocolonoscopy and biopsy (Subjects with positive IFOBT results).
Follow up	Between June 1997 and July 2004
Outcome measures	Of the 11,734 study participants who received an IFOBT test kit (OC-Hemodia), **10,573 (90.1%)** returned samples for screening. The results of **1,170 (11.1%)** of the responders were positive. Subsequently, **colonoscopy** was performed on **879 (75.1%)** of the participants with a positive test results and showed **neoplasia** in **330** participants. 54 had advanced cancer, 47 had early cancer, 131 had high-risk adenoma and 98 had low-risk adenoma. The **detection rates** and the **PPVs** were 0.95% and 8.6% for cancer, and 1.24% and 11.2% for high-risk adenoma, respectively. **Authors conclusion:** The high compliance and high detection rates for cancer and high-risk adenoma achieved in the CRC screening programme verifies the feasibility of an IFOBT in screening an average-risk population in Uruguay.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	7. Rubeca T, Rapi S, Confortini M *et al.* Evaluation of diagnostic accuracy of screening by fecal occult blood testing (FOBT). Comparison of FOB Gold and OC Sensor assays in consecutive prospective screening series. The International Journal of Biological Markers. 2006; 21(3): 157-161
Study type and Methods	Cross-sectional study The aim of the study was to evaluate the diagnostic efficacy of a recently commercialized IFOBT assay **(FOB Gold, Sentinel = SENT)** compared to the assay currently employed in the Florence screening program **(OC-Hemodia, Eiken = OC).** Screening attendees (between 50 and 69 years) from 3 municipalities of the Florence district were invited to participate in the study. Subjects with a positive IFOBT results (100 ng/ml Hb cut-off) were referred for total colonoscopy and double-contrast barium enema when colonoscopy was incomplete. The reference standard to compare the diagnostic accuracy of OC and SENT was histological diagnosis of CRC or adenoma, obtained at diagnostic colonoscopy or at further histology (operative colonoscopy, surgery). Test performance between 2 IFOBT was compared in terms of: a) positivity rate b) CRC + HRA detection rate per 1,000 screened subjects c) sensitivity, specificity, and PPV for CRC + HRA. ***HRA=high risk adenoma**
LE	3
Num. of pts and Pt characteristics	4,133 subjects (2,117 women, 2,016 men; age range 50-70 years, average age 60 years).
Intervention	IFOBT used: 1. FOB Gold, a fully automated assay developed with the Aeroset instrument (Abbott Diagnostics, USA). 2. OC-Hemodia, an automated assay developed with the 10-tube rack OC Sensor (Eiken, Tokyo, Japan).
Comparison	Total colonoscopy and double-contrast barium enema when colonoscopy was incomplete. (Subjects with positive IFOBT results).
Follow up	Between September 2003 and March 2005
Outcome measures	Of 4,133 tested subjects **190 (4.59%**) were **positive** at least at one test (OC = 140 (3.4%); SENT = 131 (3.2%)). **7 CRCs** were detected in the assessed subjects. They were **all OC positive** (crude detection rate 1.69‰, adjusted 1.88‰), whereas only **5 were SENT positive** (crude detection rate 1.21‰, adjusted 1.28‰). **48** subjects were detected as having **HRA**, **37 being OC positive** (crude detection rate 8.9‰, adjusted 9.6‰), and **32 being SENT positive** (crude detection rate 7.7‰, adjusted 8.3‰). The **relative sensitivity** for **cancer** was 100% for OC and 71.4% for SENT, whereas the relative sensitivity for **HRA** was 77.0% for OC and 66.6% for SENT. The **adjusted PPV** for **cancer** was 5.5% (crude 5.0%) for OC and 4.0% (crude 3.8%) for SENT. The adjusted PPV for **CRC+HRA** was 34.9% (crude 31.4%) for OC and 29.8% (crude 28.2%) for SENT. The **specificity** for CRC+HRA was 97.7% for both methods. None of the differences in performance between OC and SENT reached statistical significance. **Authors conclusion:** SENT assay is less sensitive than OC assay for CRC and HRA, but since the observed difference did not reach statistical significance, further study are needed for confirmation; also needed is a detailed study of the analytical aspects in order to investigate intrinsic accuracy differences between the 2 assays.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	8. Morikawa T, Kato J, Yamaji Y *et al.* Sensitivity of immunochemical fecal occult blood test to small colorectal adenomas. American Journal of Gastroenterology. 2007; 102: 2259-2264
Study type and Methods	Cross-sectional study The aim of the study was to investigate the sensitivity of IFOBT with special attention to small adenomas, using a large-scale cohort of patients who underwent colonoscopy and IFOBT. All eligible subjects were asymptomatic and participated voluntarily. They performed a 1-day IFOBT. Participants were asked to prepare a fecal sample from a stool specimen using a collection kit (Fujirebio Inc., Tokyo, Japan). They used the Magstream 1000/Hem SP automated system (Fujirebio) for IFOBT. Subjects were classified on the basis of endoscopic and pathological findings as follows: patients with no neoplasia, patients with adenomas (without invasive cancer), and patients with invasive cancer. Patients with adenomas were subdivided according to the size of the largest adenoma: ≤ 9 mm or ≥ 10 mm.
LE	3
Num. of pts and Pt characteristics	21,805 subjects (15,694 male, 6,111 female; age mean 48.2 ± 9.3 years) completed the protocol of undergoing IFOBT and colonoscopic examination.
Intervention	IFOBT used: Magstream 1000/Hem SP automated system (Fujirebio) based on the Immudia-Hem SP test (Fujirebio), which was the original version of HemeSelect (Beckman Coulter, CA).
Comparison	Colonoscopy (all subjects)
Follow up	Between April 1983 and March 2002
Outcome measures	The **sensitivity** to adenomas ≤ **9 mm** was **significantly higher** than the **false-positive rate** as revealed by analysis of all eligible subjects (7.0% vs. 4.5%, P < 0.001). Subanalysis of the sensitivity to small adenomas according to patient age and gender revealed that the test was **more sensitive** in **men than in women**, and that the sensitivity **increased as subjects aged** (6.1% in men < 50 year, 11.3% in men > 60 year). In women, on the other hand, the sensitivity to small adenomas was not significantly higher than the false-positive rate in any generation (5.1% vs. 4.7% for all eligible women, P = 0.72). **Authors conclusion:** IFOBT detected a small percentage of small adenomas at a rate that is significantly higher than the false-positive, at least in male patients.
General comments	

Evidence Table : Diagnostic accuracy
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	9. Nakama H, Zhang B, and Fattah ASMA. A cost-effective analysis of the optimum number of stool specimens collected for immunochemical occult blood screening for colorectal cancer. European Journal of Cancer. 2000; 36: 647-650
Study type and Methods	Cost-effectiveness and diagnostic accuracy The study was carried out to assess, the optimum number of fecal specimens to collect for use in IFOBT as a means of screening for CRC. For evaluation of the optimum number of sampling specimens, the results of the first day of sampling, those of the first and second day, and those of samples taken for 3 consecutive days were considered as the single-day method, the 2-day method and the 3-day method respectively. The costs of IFOBT as well as colonoscopy procedure were calculated. The average cost to detect 1 patient with CRC, the detection rate and the false-positive rate of these 3 faecal sample collection methods were evaluated and compared.
LE	II-3
Num. of pts and Pt characteristics	3,300 asymptomatic people aged over 40 years, gave samples for IFOBT and colonoscopy was carried out during a medical check-up.
Intervention	IFOBT used: Monohaem (Nihon Pharmaceutical, Japan)
Comparison	Colonoscopy (all subjects).
Follow up	
Outcome measures	**17** patients with **CRC** were diagnosed by colonoscopy. **Positive cases** of an IFOBT were 125 (3.8%), 168 (5.1%), and 191 (5.8%) in the single-day, 2-day and 3-day methods. The number of patients with **CRC detected** by **colonoscopic examination** was **8, 14 and 15** in the single-day, 2-day and 3-day methods. Accordingly, the **detection rate** and the **false-positive rate** were calculated as: **47%** and **3.5%** for the single-day method of collection **82%** and **4.7%** for the 2-days method **88%** and **5.3%** for the 3-day method Thus, there were significant differences in the detection rate between the single- and 2-day methods ($P < 0.05$) and between the single- and 3-day methods ($P < 0.05$). No significant differences in the detection rates and false-positive rates between the 2-day and 3-day methods. **Authors conclusion:** The present economic analysis suggests that the **2-day fecal collection method** is recommended for IFOBT by Monohaem from the aspects of cost-effectiveness and diagnostic accuracy.
General comments	

Evidence Table : Diagnostic accuracy (OTHER CONSIDERATIONS)
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	10. Grazzini G, Ventura L, Zappa M *et al.* Influence of seasonal variations in ambient temperatures on performance of immunochemical faecal occult blood test for colorectal cancer screening: observational study from the Florence district. Gut. 2010; 59: 1511-1515
Study type and Methods	Cohort study The aim of the study was to examine the performance of IFOBT in the Florence screening programme over several seasons to evaluate the impact of variations in ambient temperature on the performance of the screening test. Measured haemoglobin (Hb) concentrations were aggregated into seasons with their **average ambient temperature (AAT)**. Using **logistic regression,** the AAT over the period preceding the test measurement was analysed. This period included the time between faecal sampling and return of the test sample (mean 7 days) and the time in the laboratory refrigerator before analysis (mean 4 days). The AAT from days **5-11** before analysis of the test sample was considered a determinant of test positivity. A **non-parametric** test (**Kruskal-Wallis** rank test for quality) was used to evaluate the difference across the seasons. The **probability of the IFOBT being positive (Hb concentration ≥ 100 ng/ml)** and of **diagnosing a neoplastic lesion (cancer or advanced adenoma)** was studied using a logistic model adjusted for sex, age, season and episode of screening (first or repeated test).
LE	II-2
Num. of pts and Pt characteristics	A total of 199,654 IFOBT (93,191 men and 106,463 women) were performed in the CRC screening programme.
Intervention	IFOBT used: OC-Sensor Micro instrument
Comparison	Full colonoscopy during dedicated sessions at an accredited assessment clinic (Subjects with positive IFOBT results).
Follow up	8 years
Outcome measures	A total of **199,654** IFOBT results were examined. **Mean IFOBT seasonal Hb concentration (ng/ml)** were: • Spring 27.6 (95% CI: 26.2-29.1) • Summer 25.2 (95% CI: 23.1-27.3) • Autumn 29.2 (95% CI: 27.2-30.6) • Winter 29.5 (95% CI: 27.9-31.1) Logistic regression showed that there was a **17% lower probability** of the IFOBT being positive in **summer** than in **winter**. The results of the logistic regression showed that an **increased in temperature** of **1°C** produced a **0.7% reduction** in probability of a IFOBT being positive. In the summer the **probability of detecting a cancer or an advanced adenoma** was about **13% lower** than in the winter. **Authors conclusion:** The study showed that there was a significant fall in Hb concentration at higher ambient temperatures. These results will have important implications for the organisation of IFOBT-based screening programmes, particularly in countries with high ambient temperatures.
General comments	

Evidence Table : Diagnostic accuracy (OTHER CONSIDERATIONS)
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	11. van Rossum LG, van Rijn AF, van Oijen MG *et al.* False negative fecal occult blood tests due to delayed sample return in colorectal cancer screening. Int. J. Cancer. 2009; 125: 746-750
Study type and Methods	Cross-sectional study The aim of the study was to evaluate the effects of delay between sampling and laboratory delivery on IFOBT performance. A large prospective population-based screening study in more than 20,000 persons, randomly selected from general population in Netherlands. IFOBT positivity (≥ 50 ng/ml Hb) in CRC screening participants without delay (< 5 days) was compared with positivity in participants with ≥ 5 and ≥ 7 days delay. Additionally, positive tests were stored at room temperature and retested 5 times within 10-14 days. For generalizability, they also present data concerning a cut-off value of 100 ng/ml in the results. Odds ratio's (OR) and 95% CI are presented for the different between participants with delay compared with participants without delay
LE	3
Num. of pts and Pt characteristics	Screening population 50-75 years of age: **20,623** Half of the screening population was randomly allocated to receive an IFOBT: **10,322**
Intervention	IFOBT used: OC-Sensor® (Eiken, Tokyo, Japan) was processed with the OC-Mikro instrument (Eiken, Tokyo, Japan).
Comparison	Colonoscopy (Subjects with positive IFOBT results).
Follow up	From June 2006 to February 2007
Outcome measures	The IFOBT were returned by **6,157 (60%)** of the invited subjects. A total of **3,767 (61%)** participants self-reported the date of fecal sampling: in **705 (19%)** delay was ≥ **5 days** and in **195 (5%)** ≥ **7 days**. OC-Sensor tests were positive (≥ 50 ng/ml) in **265 (8.7%)** of tests delivered without delay, in **42 (6.0%)** with a delay ≥ 5 days and in **8 (4.1%)** with a delay ≥ 7 days. Compare with OC-Sensor tests returned without delay, the **positivity rate** was **significantly decreased** after a delay ≥ 5 days (**OR 0.7**; 95% CI 0.5-0.9), and after a delay ≥ 7 days (**OR 0.5**; 95% CI 0.2-0.9). They **retested positive OC-Sensor tests** (≥ 50 ng/ml) of **170** participants of which **139 (82%)** had a colonoscopy: **45 (32%)** had advanced adenomas (not CRC) and **8 (6%)** had CRC. Mean daily fecal haemoglobin decrease was **29 ng/ml** (SD 38 and median 11 ng/ml). In patients with **advanced adenomas**, haemoglobin in the sample was **< 50 ng/ml** in **5 (11%)** 2-3 days after the initial test and in **16 (36%)** after 10-14 days. Only after 7 days, **2 (25%)** of the samples of participants with CRC became false negative. **Authors conclusion:** Delay in sample return increased false negative IFOBT. Mainly precursor lesions, but also CRC, will be missed due to delayed sample return.
General comments	

Evidence Table : Diagnostic accuracy (COMPETING TECHNOLOGIES)
Question : What is the diagnostic accuracy of IFOBT in detecting CRC?

Bibliographic citation	12. Kalimutho M, Del Vecchio Blanco G, Cretella M *et al.* A simplified, non-invasive fecal-based DNA integrity assay and IFOBT for colorectal cancer detection. Int J Colorectal Dis. 2011; 26: 583-592
Study type and Methods	Cross-sectional study A prospective single-centre study was performed to evaluate the sensitivity and specificity of fecal-based DNA (fDNA) versus IFOBT and calprotectin for CRC and adenoma detection. Feces were collected from 204 subjects and DNA integrity assay (DIA) was quantified by quantitative-denaturing high performance liquid chromatography (QdHPLC). Calprotectin and IFOBT were assessed using Calprest ELISA kit and IFOBT test card (immunochromatographic sandwich assay principle), respectively. The diagnostic performance was calculated by receiver operating characteristic (ROC) curve analysis, to determine the best cut-off value for the highest sensitivity and specificity of the assays.
LE	3
Num. of pts and Pt characteristics	204 patients (age range 19 to 88 years) in Belfast, Northen Ireland, UK who came to gastroenterology unit to have a colonoscopy were recruited; 99 patients with no dysplastic lesion and 74 adenomas were found whereas 31 cancer patients were diagnosed. Exclusion criteria: diarrhea due to insufficient fecal materials, familial adenomatous polyposis, hereditary nonpolyposis CRC, and inflammatory bowel disease.
Intervention	1. fDNA analysis by polymerase chain reaction (PCR) and QdHPLC 2. IFOBT 3. Calprotectin
Comparison	Colonoscopy (all subjects).
Follow up	From December 2007 to August 2009
Outcome measures	A total of **192** fecal specimens were analysed (**28 CRC, 69 adenoma, and 95 CRC/ polyp-free).** **24 of 28** CRC patients were identified using DIA in contrast with **14 of 27** using IFOBT (**sensitivity of 86% vs. 52%** and a **specificity of 81% vs.98%,** respectively). For adenoma detection, the sensitivity of both methods turned out to be as low as **17% for DIA** and **21% for IFOBT**. To minimize false-positive cases of the developed test, area under the curve of **ROC** was evaluated such that the sensitivity and specificity of average DIA (AVG-DIA) for cancer detection were **79%** and **92%,** respectively, and for IFOBT were **52%** and **98%,** respectively. The combination of DIA with IFOBT detects the majority of CRC cases with sensitivity of **89%** and specificity of **95%,** p<0.001. The combination also improved the sensitivity of polyps, particularly high-grade dysplasia and advance adenoma (**33%, p=0.0015**) as opposed to a single evaluation assay (17%-21%). Calprotectin in the analysis was confirmed as a test with acceptable sensitivity but with lower specificity of **72%** and **75%** respectively. The cut-off value of calprotectin was 45.8 ng/ml for CRC detection. **Authors conclusions:** Study data suggest that the fDNA integrity assay by QdHPLC is a valid and feasible method with a high level of sensitivity in detecting individuals with CRC. Combination of IFOBT and fDNA to enhance the detection rate of CRC and adenoma as a screening modality option.
General comments	

Evidence Table : Effectiveness
Question : Is CRC screening using IFOBT effective in detecting and reducing mortality due to CRC?

Bibliographic citation	1. Saito H, Soma Y, Koeda J *et al.* Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. Int. J. Cancer. 1995; 61: 465-469
Study type and Methods	Case-control A case-control study to evaluate the screening was conducted in study areas where no previous and no other concomitant CRC screening had been performed. Fecal occult blood screening using a 1-day immunochemical hemagglutination test (Immudia-Hem Sp or HemeSelect: Fujirebio, Tokyo, Japan) has been performed since 1986 in Aomori Prefecture. The entire population of the 26 study areas combined was 296,439 (154,715 males, 141,724 females) at the time when the screening program was started. **Conditional logistic regression** analysis was used to calculate the **odd ratio (OR)** of dying of CRC for those screened within 1, 2, 3, 4 and 5 years before case diagnosis versus those not screened in the corresponding intervals. OR were also calculated by number of years since the most recent screening history, to study the optimal screening interval.
LE	II-2
Num. of pts and Pt characteristics	Case subjects are defined as those who: 1) died of CRC during the period between April 1, 1986 and December 31, 1992 2) were diagnosed as having CRC between the ages of 40 and 79 after the screening program was started 3) had been living in the same area since the screening program was started 4) had not had previous histories of CRC before the screening program was started in 1986 or 1987. 3 controls were randomly selected from the list of individuals who were alive at the time of diagnosis of the corresponding case and had been living in the same area as the case, matched by gender and age.
Intervention	1. CRC screening using 1-day immunochemical hemagglutination test (Immudia-Hem Sp or HemeSelect: Fujirebio, Tokyo, Japan) 2. No screening
Comparison	Total colonoscopy (Subjects with positive IFOBT results).
Follow up	Between April 1, 1986 and December 31, 1992
Outcome measures	A total of **193 cases** and **577 controls** were used in the analysis. The risk of developing fatal CRC was **reduced** by **23% to 60%** among those who had a screening history, relative to those not screened, with significant of the OR for those screened within 1, 2, and 3 years before case diagnosis. OR for those screened within 1, 2 and 3 years of case diagnostic versus those not screened were **0.40** (95% CI: 0.17-0.92), **0.41** (95% CI: 0.20-0.82), and **0.48** (95% CI: 0.25-0.92), respectively. OR gradually increased towards 1.0 as the duration during which screening histories were compared was extended, and show similar tendencies when analysed by number of years since the most recent screening history. **Authors conclusion:** These results suggest that CRC screening by the IFOBT would reduce mortality from CRC.
General comments	

Evidence Table : Effectiveness
Question : Is CRC screening using IFOBT effective in detecting and reducing mortality due to CRC?

Bibliographic citation	2. Nakajima M, Saito H, Soma Y *et al.* Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. British Journal of Cancer. 2003; 89: 23-28
Study type and Methods	Case-control A case-control study was conducted to evaluate whether screening with the IFOBT reduces the risk of developing advanced CRC in the area where annual screening with the IFOBT has been performed. CRC screening has been conducted using 1-day IFOBT test (Immudia-Hem Sp: Fujirebio, Tokyo, Japan) since 1986 in Aomori Prefecture. Screening was annually offered to all men and women, who held national health insurance, aged ≥ 40 years. Screeners who tested positive for FOBTs were recommended to undergo diagnostic investigation by total colonoscopy. **Conditional logistic regression** analysis was used to calculate the **odd ratio (OR)** of developing advanced cancer for those having at least one screening test within 2, 3, 4 and 5 years before case diagnosis versus those having no screening test in the corresponding periods. OR were also calculated for those having their most recent screening history in each of the 2-5 years, to study the optimal screening interval.
LE	II-2
Num. of pts and Pt characteristics	Case were defined as the consecutive patients clinically diagnosed as having advanced CRC that invaded to the muscularis propriae or deeper, which required surgery. For inclusion, case subjects were ≥ 40 years at the time of diagnosis and had been living in the same area since 1986 when the screening programme was started. Patients with a previous history of CRC were excluded. Potential case subjects were obtained from the files of cancer registries that cover the whole prefecture. For each case, 3 controls were randomly selected from the list of residents in 1986 in the study area, where the corresponding case lived, matched by gender, age and residential area within the town or village.
Intervention	1. CRC screening using 1-day IFOBT test (Immudia-Hem Sp: Fujirebio, Tokyo, Japan) 2. No screening
Comparison	Total colonoscopy (Subjects with positive IFOBT results).
Follow up	Between April 1, 1989 and December 31, 1992
Outcome measures	A total of **375 cases** and **1,065 controls** were used in the analysis. Risk of developing advanced CRC was **reduced** by **28% to 46%** among individuals having at least one screening within 2-4 years before case diagnosis. The OR for those screened within 2 and 3 years before the diagnosis versus those not screened was **0.60** (95% CI: 0.29-1.23), **0.54** (95% CI: 0.29-0.99), respectively, but no reduction in risk was observed after more than 3 years. Regarding **anatomic location**, the ORs of developing advanced cancer for those having al least one screening history within 2-5 years were **lower for rectum** than for **colon** (**0.32-0.73** and **0.84-1.18** for rectum and colon, respectively). **Authors conclusion:** The results suggest that a screening programme with IFOBT can be effective for prevention of advanced CRC. Risk reduction appears to be larger for rectal than for colon cancer.
General comments	

Evidence Table : Effectiveness (OTHER CONSIDERATIONS)
Question : Is CRC screening using IFOBT effective in detecting and reducing mortality due to CRC?

Bibliographic citation	3. Zorzi M, Fedato C, Grazzini G *et al.* High sensitivity of five colorectal screening programmes with faecal immunochemical test in the Veneto Region, Italy. Gut. 2011; 60: 944-949
Study type and Methods	Cohort study The aim of the study was to estimate the test and episode sensitivity of five CRC screening programmes taking place in the Veneto Region, Italy through the identification of **interval cancers (ICs)** obtained by the linkage of screening archived and hospital discharge records (HRDs). ICs were identified in subjects who had a **negative result** in a screening examination from 2002 to 2007 (N=267,769); data were linked with 2002-2008 HDRs. Analysis was based on the follow up of 468,306 person-years. The proportional incident-based sensitivity was estimated overall and by sex, age class, time since last negative IFOBT result, anatomical site, and history of screening (first or subsequent test). Sensitivity = 1-[OI(t) / EI) where OI=observed interval cancers during time t and EI=expected incident cancers.
LE	II-2
Num. of pts and Pt characteristics	267,769 screening episodes took place between 2002 and 2007 (males 47.6%), **173,859** of which were a first screening and **93,010** a subsequent one.
Intervention	Two IFOBT (latex agglutination test) are used: 1. (**OC-Hemodia**, developed with the OC-Sensor Micro instrument, Eiken, Tokyo, Japan) in 4 programmes 2. **FOB Gold** (Sentinel Diagnostics, Milan, Italy) in 1 programme Positivity threshold of 100 ng Hb/ml of sample solution.
Comparison	Colonoscopy (or, when a complete colonoscopy is not possible, a double-contrast barium enema x-ray) is recommended to all IFOBT positive subjects.
Follow up	2 years
Outcome measures	IFOBT was positive in **13,388 (5.0%)**, subjects of which **12,093 (90.3%)** accepted to undergo recommended assessments whereas 1,295 (9.7%) refused. Complete colonoscopy was carried out in 94.2% cases. A total of **748 cancers** were detected at screening with a **detection rate** of **2.8 X 1,000 screened**. Overall, **126 ICs** were identified, compared to **572 expected cancers**. The proportional incidences were **15.3%** and **31.0%** in the first and the second interval years, respectively, with an **overall episode sensitivity** of **78.0%** (95% CI: 73.8 to 81.6). Sensitivity was **higher for males** than females **(80.1% vs 74.8%)**; no differences were observed by age, anatomical site or between programmes. The test sensitivity of IFOBT was **82.1%** (95% CI: 78.1% to 85.3%). **Authors conclusion:** IFOBT-based screening programmes showed a high performance in terms of sensitivity as estimated through the IC rates. The screening schedule utilised in the programmes (single IFOBT, positivity treshold of 100 ng Hb/ml of sample solution, inter-screening interval of 2 years) shows low rates of missed cancers that are diagnosed during the interval. HDR are convinient and realible source of data for IC studies.
General comments	

Evidence Table : Effectiveness
Question : Is CRC screening using IFOBT effective in detecting and reducing mortality due to CRC?

Bibliographic citation	4. Yang H, Ge Z, Dai J *et al.* Effectiveness of the immunofecal occult blood test for colorectal cancer screening in a large population. Digestive Disease Sci. 2011; 56: 203-207
Study type and Methods	Cross-sectional study The aim of the study was to evaluate the effectiveness of IFOBT for the screening of precancerous lesions and CRC. IFOBT was performed on 5,919 adults who received periodic health examination in the health care centre of Renji Hospital, Shanghai. The threshold of the test was set at 100 ng/ml of Hb. Measurement data were expressed as mean ± SD, and enumeration data were expressed as frequency distribution tables.
LE	3
Num. of pts and Pt characteristics	A total of 5,919 cases (3,268 men and 2,651 women; mean age 55.18 ± 15.67 years) who received periodic health examination including IFOBT. The exclusion criteria were as follows: (1) cases with gingival hemorrhage, epistaxis, menses, anal fissure, hemorrhoid, and other diseases that could influence the test result; (2) patients who were reluctant to provide fecal samples; and (3) patients who refused colonoscopy and/or double-contrast barium enema examinations.
Intervention	IFOBT was performed using an OC-MICRO™ instrument (Eiken, Tokyo, Japan).
Comparison	Colonoscopy and a double-contrast barium enema. (Subjects with positive IFOBT results). Diagnosis was confirmed by histopathological analysis (All pathologist were blinded to the IFOBT results).
Follow up	From July 2006 to June 2007
Outcome measures	At least one positive result was found in each of **314 out of 5,919** cases for IFOBT, where 201 cases (64.01%) were male and 113 cases (35.99%) were female. **Positive rate** was **5.30%** (314/5,919). Further examination were made in **264 IFOBT-positive cases**. Of these **116** cases with: CRC (**16** cases) or precancerous lessions (**94** cases with colorectal adenomatous polyps and **6** cases with active ulcerative colitis) were detected. The **total detection rate** of CRC and precancerous lesions was **43.94%** (116/264). TNM classification of 16 CRC cases was as follows: TNMI in 8 cases (50.00%), TNMII in 7 cases (43.75%), and TMIII in 1 cases (6.25%), indicating IFOBT can detect CRC in the early stages. **Authors conclusion:** Regular IFOBT can detect precancerous lesions and CRC in early stages and can thus reduce mortality from CRC.
General comments	

Evidence Table : Economic evaluation
Question : What is the cost/cost-effectiveness of using IFOBT for CRC screening?

Bibliographic citation	1. Nakama H, Zhang B, and Fattah ASMA. A cost-effective analysis of the optimum number of stool specimens collected for immunochemical occult blood screening for colorectal cancer. European Journal of Cancer. 2000; 36: 647-650
Study type and Methods	Cost-effectiveness and diagnostic accuracy The study was carried out to assess, the optimum number of fecal specimens to collect for use in IFOBT as a means of screening for CRC. For evaluation of the optimum number of sampling specimens, the results of the first day of sampling, those of the first and second day, and those of samples taken for 3 consecutive days were considered as the single-day method, the 2-day method and the 3-day method respectively. The costs of IFOBT as well as colonoscopy procedure were calculated. The average cost to detect 1 patient with CRC, the detection rate and the false-positive rate of these 3 faecal sample collection methods were evaluated and compared.
LE	
Num. of pts and Pt characteristics	3,300 asymptomatic people aged over 40 years, gave samples for IFOBT and colonoscopy was carried out during a medical check-up.
Intervention	IFOBT used: Monohaem (Nihon Pharmaceutical, Japan)
Comparison	Colonoscopy (all subjects)
Follow up	
Outcome measures	**Cost per slide for each IFOBT** was **US $3.64** and the cost of **colonoscopic examination** for **one person** was **US $136.36**. The **average costs** for one cancer case detected were calculated as: **$3,360.68** for the single-day method, **$3,350.65** for the 2-day method and **$4,136.36** for the 3-day method, respectively. **Authors conclusion:** The present economic analysis suggests that the **2-day fecal collection method** is recommended for IFOBT by Monohaem from the aspects of cost-effectiveness and diagnostic accuracy.
General comments	

Evidence Table : Economic evaluation
Question : What is the cost/cost-effectiveness of using IFOBT for CRC screening?

Bibliographic citation	2. Nakama H, Zhang B, and Zhang X. Evaluation of the optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer. European Journal of Cancer. 2001; 37: 398-401
Study type and Methods	Cost-effectiveness and diagnostic validity These study was carried out to assess the optimum cut-off point for IFOBT (OC-Hemodia) using a 2-day method as a means of screening for CRC. The costs of IFOBT as well as colonoscopy procedure were calculated. The average cost to detect 1 patient with CRC, and the sensitivity and specificity of these 3 cut-off point of fecal haemoglobin were evaluated.
LE	
Num. of pts and Pt characteristics	4,260 asymptomatic people aged over 40 years, gave samples for IFOBT and colonoscopy was carried out during a medical check-up.
Intervention	IFOBT used: OC-Hemodia with three cut-off levels of fecal haemoglobin were used: 50, 150, and 300 ng/ml.
Comparison	Colonoscopy (all participants)
Follow up	Between April 1990 and March 1999
Outcome measures	**Cost per slide for each IFOBT** was **US $3.64** and the cost **of colonoscopic examination for one person** was **US $136.40**. The **average costs** for one cancer case detected were calculated as: **$2,870.45** for the cut-off point of 50 ng/ml, **$2,492.98** for the 150 ng/ml level, and **$3,329.09** for the 300 ng/ml level, respectively. **Author conclusion:** The findings indicated that the cut-off point of **150 ng/ml** fecal haemoglobin is recommended for IFOBT by OC-Hemodia, from the viewpoints of cost-effectiveness, as well as diagnostic validity.
General comments	

Evidence Table : Economic evaluation
Question : What is the cost/cost-effectiveness of using IFOBT for CRC screening?

Bibliographic citation	3. Li SC, Chao SL, Shu HC *et al.* Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16). Journal of Medical Screening. 2007; 14: 191-199
Study type and Methods	Cost-effectiveness analysis The optimal cut-off point of IFOBT applied to a Taiwan population-based screening for CRC was determined by receiver operating characteristics (ROC) curve analysis and further assessed by cost-effectiveness analysis (**Markov decision model and Markov cohort simulation)**. Data from screen-detected cases were collected for the cut-off above 100 ng/ml and obtained interval cancer from a nationwide cancer registry for a cut-off below 100 ng/ml. Economic evaluation was further applied to identifying the optimal cut-off by assessing the minimum incremental cost-effectiveness ratio (ICER), an indicator for cost per life year gained (effectiveness), given a series of cut-offs of IFOBT, ranging from 30 to 200 ng/ml compared with no screening.
LE	
Num. of pts and Pt characteristics	A total of 56,968 subjects (including 21,502 men and 35,466 women) were enrolled in the KCIS screening programme (data used for producing ROC curve analysis). Out of 56,968 subjects, 22,672 subjects aged 50 years or older were invited annually to have an uptake of IFOBT (58% were woman). The mean age was 63.36 ± 9.20 years. The model had a hypothetical cohort from people aged 50-80 years with population size and the make-up of demographic characteristic identical to subjects in the KCIS programme.
Intervention	1-day IFOBT method with a brush-type sampler was given to each eligible subject The stool sample was uploaded to the automated machine to yield a series of quantitative readings of IFOBT value.
Comparison	Colonoscopy (Subjects with positive IFOBT results).
Follow up	
Outcome measures	**Economic analysis** For 'no screening' (the baseline group), the **average discounted life years** and **costs** were **13.7797** and **2005.40**. Compared with the baseline group, the screening programme irrespective of any cut-off dominated over the control group indicated by minus ICER (less cost and more effectiveness). Given 100% attendance rate, **ICER had the lowest value** at **110 ng/ml** at which average discounted life years and costs were **13.83** and **1100.10**, which yielded an average of **0.0054 life year gained** and that of **cost-saving** by **905.30 (US$).** **Author conclusion:** They used cost-effectiveness to identify 110 ng/ml as the optimal cut-off of IFOBT in a Taiwanese population-based screening for CRC. Their model provides a useful approach for health policy-makers in designing population-based screening for CRC to determine the optimal cut-off of IFOBT when cost and effectiveness need to be taken into account.
General comments	

Evidence Table : Economic evaluation
Question : What is the cost/cost-effectiveness of using IFOBT for CRC screening?

Bibliographic citation	4. Telford J, Levy A, Sambrook J *et al.* The cost-effectiveness of screening for colorectal. CMAJ. 2010; 182(12): 1307-1313
Study type and Methods	Cost-effectiveness analysis Objective: To estimate the incremental cost-effectiveness of 10 strategies for CRC screening, as well as no screening program. **Probabilistic Markov model** was used to estimate the costs and quality-adjusted life expectancy of 50 year-old average risk Canadians without screening and with screening by each test. They populated the model with data from the published literature and calculated costs from the perspective of a third-party payer, with inflation to 2007 Canadian dollars.
LE	
Num. of pts and Pt characteristics	100,000 average risk Canadians aged 50 years
Intervention	3 screening strategies: 1. Low-sensitivity gFOBT (performed annually) 2. FIT (performed annually) 3. Colonoscopy (performed every 10 years) These 3 tests are currently being used or considered for population-based screening of average-risk individuals in some Canadian provinces and **reduced** the **incidence of CRC** by **44%, 65%, and 81%**, and **mortality** by **55%, 74%, and 83%**, respectively.
Comparison	No screening
Follow up	
Outcome measures	**The mean discounted costs**: i)$783 with no screening ii)$1,415 with low-sensitivity gFOBT annually iii)$1,437 with FIT annually iv)$1,529 with colonoscopy every 10 years **The mean quality-adjusted life-years**: i)15.20 with no screening ii) 15.26 with low-sensitivity gFOBT annually iii)15.30 with FIT annually iv)15.32 with colonoscopy every 10 years **ICER**: These 3 screening strategies were cost-effective in comparison with no screening, generated ICER of $**9,159, $611, and $6,133** per quality-adjusted life year, respectively. The findings were robust to probabilistic sensitivity analysis. **Authors conclusion:** Screening of average-risk individual for CRC is a cost-effective measure, even with less-than-perfect compliance. Recognizing that decisions about screening for CRC depend on local resources and individual patient preferences, either an annual high-sensitivity fecal test, such as a FIT, or colonoscopy every 10 years offer good value for money in Canada.
General comments	

Evidence Table : Economic evaluation
Question : What is the cost/cost-effectiveness of using IFOBT for CRC screening?

Bibliographic citation	5. Heitman S, Hilsden R, Au F *et al.* Colorectal cancer screening for average-risk North Americans: an economic evaluation. Economic of Colorectal Cancer Screening. 2010; 7(11): 1-13
Study type and Methods	An incremental cost-utility analysis Objective: To perform an economic evaluation of CRC screening in average risk North American individuals considering all relevant screening modalities and current CRC treatment costs. An incremental cost-utility analysis using a **Markov model** was performed to compare **6 screening strategies, as well as no screening** natural history arm. For the baseline data of the model, they used adenoma and colorectal prevalence rates from a recent systematic review and based screening adherence, test performance, and colorectal treatment costs on available data. The outcome measures included lifetime costs, number of cancers, cancer-related deaths, quality-adjusted life-years gained, and incremental cost-utility ratios. Sensitivity and scenario analysis were performed. All costs are reported in 2008 CAN$
LE	
Num. of pts and Pt characteristics	Among 100,000 average-risk individuals, aged 50-75 years.
Intervention	6 screening strategies: 1.gFOBT annually 2.FIT annually 3.Fecal DNA every 3 years 4.Flexible sigmoidoscopy every 5 years 5.Computed tomographic colonography (CTC) every 5 years 6.Colonoscopy every 10 years They considered 3 distinct FIT strategies on the basis of assays and collection methods taken from studies that have reported “low”, “mid”, and “high” test performance characteristics.
Comparison	No screening
Follow up	
Outcome measures	Annual CRC screening using **FIT**, assuming **mid-range** test performance characteristics, was **more effective** and **less costly** compared to all strategies (including no screening) except FIT-high. Using this screening modality (FIT-mid), among the lifetimes of 100,000 average-risk patients, the number of cancers could be **reduced** from **4,857 to 1,393 (71%)** and the number of **CRC deaths from 1,782 to 457 (74%)**, while saving **CAN$68 per person.** Although in the sensitivity and scenario analysis, screening patients using FIT became more expensive than a strategy of no screening when the test performance of FIT was reduced, or the cost of managing CRC was lowered, CRC screening with FIT remained the most economically attractive screening option. **Authors conclusion:** This model-based economic analysis found that FIT is more effective and less costly than all other colorectal screening strategies. Furthermore, this study suggests that annual screening with FIT (assuming mid-range test performance characteristics) reduced the risk of CRC and CRC-related death, and lower health care costs in comparison to all other screening strategies and to no screening. Therefore, health policy makers should consider prioritizing funding for FIT as the screening modality for CRC.
General comments	

APPENDIX 7

LIST OF EXCLUDED STUDIES

1. Hundt S, Haug U, and Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Annals of Internal Medicine. 2009; 150: 162-169
2. Haug U, Hundt S, and Brenner H. Quantitative immunochemical fecal occult blood testing for colorectal adenoma detection: Evaluation in the target population of screening and comparison with qualitative tests. Am J Gastroenterol. 2010; 105: 682-690
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APPENDIX 8

PERTINENT DETAILS OF THE INCLUDED DIAGNOSTIC ACCURACY STUDIES

Study	Year	Country / region	IFOBT brand names	Level of Hb for positive test results	PPV %		Sensitivity % (95% CI)		Specificity % (95% CI)		Detection per 1,000 screened (95% CI)	
					Cancer	HRA	Cancer	HRA	Cancer	HRA	Cancer	HRA
Castiglione G et al.	2000	Italy	1. Immudia Hem-Sp or Hemeselect 2. OC-Hemodia (Interpreted using automated analyzer, OC-Sensor)	- 100 ng/ml 150 ng/ml 200 ng/ml	NS NS NS NS	NS NS NS NS	-	-	-	-	2.9 2.7 2.6 2.4	4.8 5.4 4.9 4.2
Castiglione G et al.	2002	Italy	1. OC-Hemodia (Interpreted using automated analyzer, OC-Sensor)	100 to 200 ng/ml	9.0 to 13.4 (first) 5.5 to 10.9 (subsequent)	21.3 to 28.9 (first) 16.6 to 18.5 (subsequent)	-	-	-	-	3.3 to 2.7 (first) 1.6 to 1.4 (subsequent)	7.9 to 5.9 (first) 4.9 to 2.3 (subsequent)
Nakama H et al.	2001	Japan	1. OC-Hemodia (Interpreted using automated analyzer, OC-Sensor)	50 ng/ml 150 ng/ml 300 ng/ml	8.6 12.6 10.8	NR NR NR	89.0 81.0 56.0	NR NR NR	94.0 96.0 97.0	NR NR NR	NR NR NR	NR NR NR
Li SC et al.	2007	Taiwan	1. OC-Hemodia (Interpreted using automated analyzer, OC-Sensor)	100 ng/ml	NR	NR	81.5	NR	94.3	NR	NR	NR
Crotta S et al.	2004	Italy	1. OC-Hemodia (Interpreted using automated analyzer, OC-Sensor)	100 ng/ml	4.5	40.3	-	-	-	-	1.8	16.6
Fenocchi et al.	2006	Uruguay	1. OC-Hemodia (Interpreted using automated analyzer, OC-Sensor II)	100 ng/ml	8.6	11.2	-	-	-	-	9.5	12.4
Morikawa T et al.	2007	Japan	1. Magstream 1000/ Hem SP	NR	34.0	-	28.5	-	86.4	-	NR	NR
					PPV %		Sensitivity % (95% CI)		Specificity % (95% CI)			
					Cancer	Cancer + HRA	Cancer	Cancer + HRA	Cancer	Cancer + HRA		
Rubeca T et al.	2006	Italy	1. FOB Gold 2. OC-Hemodia (Interpreted using automated analyzer, OC-Sensor)	100 ng/ml	5.0 3.8	28.2 31.4	-	-	NR NR	97.7 97.7	1.7	1.2

NS: Not significant NR: Not reported HRA: High risk adenoma

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia,
Level 4, Block E1, Complex E, Precinct 1,
Federal Government Administrative Centre
62590, Putrajaya, Malaysia
Tel: 03 - 8883 1246/47
Fax: 03 - 8883 1230

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