Immunochemical Faecal Occult Blood Test for Colorectal Cancer Screening: A Systematic Review

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SUMMARY
A systematic review on the effectiveness and cost-effectiveness of Immunochemical faecal occult IFOBT for CRC screening was carried out. A total of 450 relevant titles were identified, 41 abstracts were screened and 18 articles were included in the results. There was fair level of retrievable evidence to suggest that the sensitivity and specificity of IFOBT varies with the cut-off point of haemoglobin, whereas the diagnostic accuracy performance was influenced by high temperature and haemoglobin stability. A screening programme using IFOBT can be effective for prevention of advanced CRC and reduced mortality. There was also evidence to suggest that IFOBT is cost-effective in comparison with no screening, whereby a two-day faecal collection method was found to be cost-effective as a means of screening for CRC. Based on the review, quantitative IFOBT method can be used in Malaysia as a screening test for CRC. The use of fully automated IFOBT assay would be highly desirable.

KEY WORDS:
Systematic review, IFOBT, colorectal cancer screening

INTRODUCTION
CRC 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] While more recent data is yet to be published, going by the numbers provided in the National Cancer Registry (NCR) in 2006; CRC was then already ranked the second most common cancer after breast cancer in Malaysia. It is the first among male and also second among females.[2]

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 commercially available FOBTs: the long established guaiac test (gFOBT) and the newer IFOBT, available either qualitative or quantitative methods.[3]

The diagnosis of CRC raises many questions and there is a need for clear, understandable answer. The most widely used screening strategy in the average risk population remains the gFOBT whose efficacy was shown in three randomised controlled trials (RCTs).[4-6] However, gFOBT which detects the peroxidise activity of 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. IFOBT that use specific antibodies against human blood components overcome the problem of diet or medication restriction.[7]

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.[8, 9]

In Malaysia, currently there is no formal/structured national CRC screening programme being implemented. At present, surgical resection continues to be the best hope of cure for patients with CRC. 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 review evidence on the effectiveness and cost-effectiveness 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.

MATERIALS AND METHODS
Electronic databases such as MEDLINE, PubMed, EBM Reviews – Cochrane Database of Systematic Reviews, EBM Reviews – Cochrane Central Register of Controlled Trials, EBM Reviews – HTA Databases, EBM Reviews – NHS Economic

Evaluation Database, EBM Full Text – Cochrane DSR, ACP Journal Club and DARE were searched for published literature pertaining to the use of IFOBT for CRC screening. Additional articles were identified by reviewing the bibliographies of retrieved articles and hand-searching of journals. Further information was sought from unpublished reports. There was no limit to the search.

Selection of studies
For this systematic review, we included all studies that met the following conditions: the study design had to be cross-sectional diagnostic accuracy, HTA reports, systematic review, randomised controlled trial (RCT), cohort, case-control, and economic evaluation. CRC screening should be conducted among adults or general population using various types of IFOBTs. Data were sought for the following primary outcome measures: diagnostic accuracy of the various types of IFOBTs, effectiveness of CRC screening using IFOBT, adverse events related to the use of IFOBT, and cost-effectiveness of using IFOBT. Studies were excluded if it was a high-risk study population, animal or experimental study. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it was absolutely clear from the title and/or the abstract that the study was not relevant, it was excluded. If it was unclear from the available 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.

Quality assessment
The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) depending on the type of study design.[10] Quality assessment was conducted by two reviewers. Disagreements were resolved by discussion. All full text articles related to effectiveness were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.[11] All full text articles related to diagnostic studies were graded according to Hierarchy of Evidence for Test Accuracy Studies, CRD Report Number 4 (2nd Edition), March 2001.[12]

Data extraction strategy
Data were extracted from included studies by a reviewer using a pre-designed data extraction form (evidence table) and checked by another reviewer. Details on methods, study population characteristics, intervention and comparator, outcomes measures for diagnostic accuracy, effectiveness, safety, cost/cost-effectiveness of tests used in the CRC screening were extracted. The extracted data were presented and discussed with the expert committee before deciding on the eligibility of articles to be included in this report.

RESULTS
A total of 450 relevant titles were identified and 347 abstracts were screened. After reading and appraising the full text articles, 18 articles were included in the results. Fifteen full text articles were excluded based on inclusion and exclusion criteria and quality of the studies. The articles comprised nine cross-sectional diagnostic accuracy studies, two cohort studies, two case-control studies, and five economic evaluation papers. The search did not yield any health technology assessment reports, systematic reviews or RCT related to the effectiveness of using IFOBT for CRC screening.

Diagnostic accuracy
Table I summarises the diagnostic accuracy of IFOBT for CRC and high risk adenoma (HRA) in nine studies. The table indicated that generally, 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 (HRA). False positive rate ranged from 1.5% to 6.0% for CRC.[13-21]

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 (Table II and Table III). 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.[22] 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.[23]

Effectiveness
A screening programme using IFOBT can be effective for prevention of advanced CRC (risk of developing advanced CRC was reduced by 28.0% to 46.0%) and reduction the risk of developing fatal CRC by 23.0% to 60.0%.[24, 25] Regular IFOBT can detect precancerous lesions and CRC in early stages and thus reduce mortality from CRC[26] (Table IV).

Safety
There was no retrievable evidence from the scientific databases on adverse events associated with IFOBTs used for CRC screening. However, the use of IFOBTs in a screening setting is likely to increase the number of colonoscopies performed in the screened population. It is expected that the adverse events associated with these procedure will also be increased. In the large RCT's of the gFOBT screening programmes, there was a recognised complication rate from colonoscopies undertaken in FOBT positive cases. Complications of colonoscopies are a downside in any screening programme that inevitably generates a large number of colonoscopies, a significant proportion of which would be undertaken in subjects with false positive FOBT results. Several test methods on IFOBT have United States Food & Drug Administration (US FDA) approval.[27]

Cost/cost effectiveness
A two-day faecal collection method was found to be more cost-effective (least expensive) compared to one-day and three-day faecal collection method for use in IFOBT as shown in Table V, as a means of screening for CRC.[15] Nakama *et al.* 2001 indicated that the cut-off point of 150 ng/ml faecal haemoglobin is recommended for IFOBT, from the viewpoints of cost-effectiveness, as well as diagnostic validity.[13] Table VI

Table I: Diagnostic accuracy of IFOBT for CRC screening

Authors / study designs	Sample sizes	IFOBT brand names	Cut-off point of Hb (ng/mL)	Diagnostic accuracy
Nakama *et al.* 2001, Japan (13) / Cost-effectiveness and diagnostic validity	4,260 asymptomatic peoples; aged over 40 years	OC-Hemodia with OC-Sensor	50, 100	Sensitivity & specificity were reported as:- 89.0% & 94.0% for 50 ng/ml 81.0% & 96.0% for 150 ng/ml
Li SC *et al.* 2007, Taiwan (14) / Cost-effectiveness analysis	56, 968 subjects; mean aged 63.36 ± 9.20 years	OC-Hemodia with OC-Sensor	100	Sensitivity: 81.5% (95% CI: 70.2% to 89.2%) False positive: 5.7% (95% CI: 5.4% to 6.0%)
Nakama *et al.* 2000, Japan (15) / Cost-effectiveness and diagnostic accuracy	3,300 asymptomatic peoples; aged over 40 years	Monohaem (qualitative)	-	Detection rate & false positive rate were reported as:- 47.0% & 3.5% for the single-day method 82.0% & 4.7% for the two-days method 88.0% & 5.3% for the three-days method
Castiglione G *et al.* 2000, Italy (16) / Cross-sectional study	5,884 subjects (2,997 women, mean age 59.6; 2,867 men, mean age 59.5)	1. Immudia Hem-Sp or Hemeselect (qualitative) 2. OC-Hemodia (quantitative)	100, 150, 200	Positivity rate: OC-Hemodia 100 ng/ml: (3.5% 95% CI: 3.1% to 4.0%) Immudia Hem-Sp: (3.3% 95% CI: 2.9% to 3.8%) PPV : No significant difference between test
Castiglione G *et al.* 2002, Italy (17) / Cross-sectional study	11,774 subjects (6,063 women, mean age 59.1; 5,711 men, mean age 59.2)	OC-Hemodia with OC-Sensor	100-200	Progressively increasing the positivity threshold showed:- an increased in PPV for CRC: 9.0% to 13.4% an increased in PPV for HRA: 21.3% to 28.9%
Crotta S *et al.* 2004, Italy (18) / Cross-sectional study	2,961 subjects (1,403 males, 1,558 females) aged 50-74 years	OC-Hemodia with OC-Sensor	100	PPV for CRC & HRA were 4.5% & 40.3%
Fenocchi *et al.* 2006, Uruguay (19) / Cross-sectional study	11,734 (3,663 men, mean age 61.3 ± 9.6 years; 8,071 women, mean age 61.2 ± 9.1 years)	OC-Hemodia with OC-Sensor II	100	PPV of 8.6% & 11.2% for CRC & HRA
Rubeca T *et al.* 2006, Italy (20) / Cross-sectional study	4,133 subjects (2,117 women, 2,016 men; age range 50-70 years)	1. FOB Gold (SENT) 2. OC-Hemodia (OC)	100	PPV for CRC was 5.0% for OC & 3.8% for SENT PPV for CRC+HRA was 31.4% for OC & 28.2% for SENT
Morikawa T *et al.* 2007, Japan (21) / Cross-sectional study	21,805 subjects (15,694 male, 6,111 female; age mean 48.2 ± 9.3 years)	Magstream 1000/Hem SP	Not reported	PPV for CRC was 34.0%

Abbreviations:

IFOBT	Immunochemical faecal occult blood test
CRC	Colorectal cancer
HRA	High risk adenoma
ng/mL	nano gram per millilitre
Hb	Haemoglobin
PPV	Positive predictive value
CI	Confident interval

Table II: Effect of variation in ambient temperature (Hb stability)

Authors / study designs	Sample sizes	IFOBT brand names	Cut-off point of Hb (ng/mL)	Finding/outcomes
Grazzini et al. 2010 Italy (22) / Cohort study	199,654 IFOBT (93,191 men and 106,463 women)	OC-Sensor Micro	≥ 100	Mean IFOBT seasonal haemoglobin concentration were: 27.6 ng/ml in spring (95% CI: 26.2 to 29.1) 25.2 ng/ml in summer (95% CI: 23.1 to 27.3) 29.2 ng/ml in autumn (95% CI: 27.2 to 30.6) 29.5 ng/ml in winter (95% CI: 27.9 to 31.1)

Abbreviations:
IFOBT   Immunochemical faecal occult blood test
ng/mL   nano gram per millilitre
Hb   Haemoglobin
CI   Confident interval

Table III: Effect of delayed sample returns (Hb degradation)

Authors / study designs	Sample sizes	IFOBT brand names	Cut-off point of Hb (ng/mL)	Finding/outcomes
van Rossum et al. 2009, Netherlands (23) / Cross-sectional study	20,623 screening population 50-75 years of age	OC-Sensor Micro	≥ 50	Positivity rate was significantly decreased after a delay ≥ 5 days (OR 0.7; 95% CI 0.5 to 0.9), and ≥ 7 days (OR 0.5; 95% CI 0.2 to 0.9).

Abbreviations:
IFOBT   Immunochemical faecal occult blood test
Hb   Haemoglobin
ng/mL   nano gram per millilitre
OR   Odd ratio
CI   Confident interval

Table IV: Effectiveness of IFOBT for detection the risk of developing advanced CRC, fatal CRC, and detection of precancerous lesions

Authors / study designs	Sample sizes	IFOBT brand names	Cut-off point of Hb (ng/mL)	Finding/outcomes
Nakajima M et al. 2003, Japan (24) / Case-control	375 cases and 1,065 control	Immudia Hem-Sp or Hemeselect (qualitative)	-	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
Saito H et al. 1995, Japan (25) / Case-control	193 cases and 577 control	Immudia Hem-Sp or Hemeselect (qualitative)	-	Risk of developing fatal CRC was reduced by 23.0% to 60.0% among those who had a screening history, relative to those not screened
Yang H et al. 2011, Shanghai (26) / Cross-sectional study	5,919 cases (3,268 men and 2,651 women; mean age 55.18 ± 15.67 years)	OC-MICRO™	100	TNM classification of 16 CRC cases was as follows: TNMI in eight cases (50.0%) TNMII in seven cases (43.8%) TNMIII in one case (6.3%)

Abbreviations:
IFOBT   Immunochemical faecal occult blood test
CRC   Colorectal cancer
Hb   Haemoglobin
ng/ml   nano gram per millilitre
TNM   Tumour Nodes Metastasis

Table V: Comparison of the average costs per patient with CRC detected for three faecal collection methods and three cut-off points of faecal Hb in the immunochemical faecal occult blood screening

Authors / study designs	Sample sizes	IFOBT brand names	Faecal collection method	Average costs per case detected (USD$)
Nakama et al. 2000, Japan (15) / Cost-effectiveness and diagnostic accuracy	3,300 asymptomatic peoples; aged over 40 years	Monohaem	Single-day 2-day 3-day	3,630.68 3,350.65 4,136.36
Authors / study designs	**Sample sizes**	**IFOBT brand names**	**Cut-off points (ng/mL)**	**Average costs per case detected (USD$)**
Nakama et al. 2001, Japan (13) / Cost-effectiveness and diagnostic validity	4,260 asymptomatic peoples; aged over 40 years	OC-Hemodia	50 150 300	2,870.45 2,492.98 3,329.09

Abbreviations:
IFOBT   Immunochemical faecal occult blood test
CRC   Colorectal cancer
Hb   Haemoglobin
ng/mL   nano gram per millilitre

Table VI: Economic evaluation studies

Authors / study designs	Sample sizes	Screening methods	Cancer overall	Cancer death	Cost of screening and managing CRC (CAN$)
Heitman S et al. 2010, Canada (28) / Incremental cost-utility analysis	100,000 average-risk individuals, aged 50-75 years	IFOBT – 2-days No screening	1,393 4,857	457 1,782	1,833 1,901
Authors / study designs	**Sample sizes**	**Screening methods**	**ICER (CAN$)**		
Telford J et al. 2010, Canada (29) / Cost-effectiveness analysis	100,000 average risk Canadians aged 50 years	gFOBT IFOBT Colonoscopy No screening	9,159 611 6,133 6,540		
Authors / study designs	**Sample sizes**	**Screening methods**	**Average discounted cost (USD$)**	**Average discounted life-years**	**ICER (USD$)**
Li SC et al. 2007, Taiwan (14) / Cost-effectiveness analysis	56,968 subjects; mean aged 63.36 ± 9.20 years	IFOBT No screening	1,100.10 2,005.40	13.826 13.772	16,764.81

Abbreviations:
IFOBT   Immunochemical faecal occult blood test
CRC   Colorectal cancer
gFOBT   guaiac faecal occult blood test
ICER   Incremental cost-effectiveness ratio

on the other hand summarises the economic evaluation studies of using IFOBT for CRC screening. Heitman S *et al.* 2010 revealed that by using IFOBT with 2-days faecal collection method, 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.[28] Generally, IFOBT was cost-effective in comparison with no screening. The generated ICERs were USD$16,764 and CAN$611 per quality-adjusted life year in Taiwan and Canada, respectively.[14, 29]

DISCUSSION
Overall, the studies that assessed the diagnostic accuracy or performance of IFOBT showed that it was effective for the detection of CRC and HRA. Because the test is quantitative, a concern about the optimal cut-off points was raised. Many of the studies in the review indicated that the recommended cut-off points varied from 100 ng/ml to 150 ng/ml.[13-21] Since

studies have revealed that the diagnostic accuracy of IFOBT was influenced by high temperature and lag time before the faecal sample is analyzed, 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.[22, 23]

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.[4-6] 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 developing fatal CRC by 23.0% to 60.0%.[25] 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%).[24] One study reported that regular IFOBT can detect precancerous lesions and CRC in early stages and thus reduce mortality from CRC.[26]

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.[4-6] 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.[15] There was also evidence to suggest that IFOBT was cost-effective in comparison with no screening.[14, 28-29]

LIMITATIONS
Although there was no restriction in language during the search 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.

CONCLUSION
In conclusion, there was fair level of retrievable evidence to suggest that the sensitivity and specificity of IFOBT varies with the cut-off point of haemoglobin, whereas the accuracy performance was influenced by high temperature and haemoglobin stability. A screening programme using IFOBT can be effective for prevention of advanced CRC and reduced mortality. There was also evidence to suggest that IFOBT is cost-effective in comparison with no screening, whereby a two-day faecal collection method was found to be cost-effective as a means of screening for CRC. Based on the review, quantitative IFOBT method 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. However, one has to take cognizance of the staff with the skills required to use the automated equipment that they must be well trained.

ACKNOWLEDGEMENTS

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