



Title	Alternatives to colonoscopy for population-wide colorectal cancer screening
Author(s)	Leung, WC; Foo, CC; Chan, TT; Chiang, MF; Lam, AH; Chan, HH; Cheung, CC
Citation	Hong Kong Medical Journal, 2016, v. 22 n. 1, p. 70-77
Issued Date	2016
URL	http://hdl.handle.net/10722/229491
Rights	Hong Kong Medical Journal. Copyright © Hong Kong Academy of Medicine Press.; This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

Alternatives to colonoscopy for population-wide colorectal cancer screening

William CY Leung *, Dominic CC Foo, TT Chan, MF Chiang, Allan HK Lam, Heywood HW Chan, Chris CL Cheung

ABSTRACT

Colorectal cancer is one of the top three cancers in the world in terms of incidence. Colonoscopy, which many regard as the gold standard in diagnosis of colonic polyps and neoplasm, is costly, invasive and labour-intensive, and deemed an unsuitable population-wide index screening tool. Alternative modalities, including guaiac and immunohistochemical faecal occult blood tests, computed tomographic colonography, colon capsule endoscopy, flexible sigmoidoscopy, and double-contrast barium enema are available. The procedures, test characteristics, and their implications are reviewed. Immunohistochemical faecal occult blood testing appears to be the most suitable population-wide screening test for an average-risk population, with flexible sigmoidoscopy as an alternative. More evidence is needed to determine the role of

computed tomographic colonography and colon capsule endoscopy in colorectal cancer screening.

Hong Kong Med J 2016;22:70–7

DOI: 10.12809/hkmj154685

¹ WCY Leung *

² DCC Foo, MRCSEd, FHKAM (Surgery)

¹ TT Chan

¹ MF Chiang

¹ AHK Lam

¹ HHW Chan

¹ CCL Cheung

¹ Li Ka Shing Faculty of Medicine

² Department of Surgery, Li Ka Shing Faculty of Medicine
The University of Hong Kong, Pokfulam, Hong Kong

* Corresponding author: cywleung.hku@gmail.com

This article was
published on 8 Jan
2016 at www.hkmj.org.

Introduction

Colorectal cancer (CRC) became the second and third most common cancer in women and men in 2012.¹ Most cases of CRC arise from adenoma, the process known as the adenoma-carcinoma sequence, and are therefore amenable to screening and early treatment.^{2–4} Ecological studies have shown that 2.6% to 5.6% of advanced adenoma progress to CRC annually.⁵

Colonoscopy remains the gold standard for diagnosis,⁶ and has even been used as a primary screening method in some countries (eg the US). Nonetheless its use in most countries as an index tool for mass screening of an average-risk population is impractical due to its cost, invasiveness, and need for expertise (ie endoscopists).

In this study, we reviewed the literature about the procedures, test characteristics, and implications of the following alternative screening modalities: guaiac faecal occult blood testing (gFOBT), immunohistochemical faecal occult blood testing (iFOBT), computed tomographic colonography (CTC), colon capsule endoscopy (CCE), flexible sigmoidoscopy (FS), and double-contrast barium enema (DCBE).

Guaiac faecal occult blood testing

The gFOBT offers the strongest evidence as a suitable

screening tool for CRC. Its mechanism involves detection of haemoglobin in the stool. The test is not specific for human haemoglobin however, and false-positive results can arise due to plant peroxidases and heme in red meat. False negatives can occur when stool contains certain chemicals, eg vitamin C. It also detects bleeding from the gastro-intestinal (GI) tract other than the colon and rectum. Two or more samples are usually required.

Four large-scale randomised controlled trials (RCTs) of gFOBT with long-term follow-up have been conducted; they include Minnesota study in the US,⁷ Nottingham trial in the UK,⁸ Göteborg study in Sweden,⁹ and Funen study in Denmark.¹⁰ A total of 328 767 individuals, aged 45 to 80 years, were involved. The results consistently showed reduction in CRC mortality by 12% to 33%, after up to 30 years of follow-up.^{7–10} The results are summarised in Table 1.

In screening for significant or advanced adenoma, test sensitivity was 23.8%,¹¹ and specificity was 97.7% to 99.0% with positive predictive values (PPVs) of 39.0% to 55.3%. The detection rate in intention-to-screen (ITS) analysis was 0.6% and that in per protocol (PP) analysis was 1.2%. The NNScreen, or the number of average-risk individuals needed to recruit in a screening programme to detect one advanced adenoma, was 84 to 181.^{12,13} The NNScope, or the number of colonoscopies needed to diagnose an advanced adenoma after

screening revealed a likely significant lesion, was 2.2.¹² Although NNScreen is useful in assessing each modality individually, NNScope of a test provides additional information about the role of gFOBT in a screening programme to select patients for further diagnostic colonoscopy. For CRC, the sensitivity was 54.2%, and specificity ranged from 96.9% to 98.1% with a PPV of 5.2% to 13.6%. Detection rate in ITS analysis was 0.1%, while that in PP analysis was 0.2%. The NNScreen was 392 to 936 and the NNScope was 10.3.¹¹⁻¹⁴

The Funen study¹⁰ showed the CRC mortality dropped from 18% to 11% after five screening rounds, as a result of decreased compliance. Similar findings were echoed in the Tenerife study in Spain.¹¹

Immunochemical faecal occult blood testing

The iFOBT employs an antibody-based assay, detecting globin or early degradation products of human haemoglobin.¹⁵ The antibodies used are human-specific, thus the number of false positives due to non-human blood is minimised. As globin is more rapidly degraded than heme throughout the GI tract, less upper GI tract bleeding is detected. It requires no dietary restrictions¹⁶ and has a participation rate of 38.9% to 71.9%.¹⁷⁻¹⁹ The results can be qualitative or quantitative.²⁰ Sampling technique, distribution of blood in faeces, and sample instability make true quantification difficult, however.¹⁵ Adjustment of performance parameters is possible by altering the cut-off values. It is generally agreed that a cut-off of 75 ng/mL provides a balance between higher detection rate and lower NNScope.^{12,15,18,21,22} It should also be noted though that different brands of iFOBT kits may yield different results even when the same cut-off is used.

The iFOBT on one or two consecutive faecal samples is recommended. A study showed that 1-day sampling had a higher miss rate for CRC compared with 2-day sampling.²³ Another study showed that

全民大腸癌篩查：大腸鏡檢查的替代方案

梁俊彥、傅志聰、陳子泰、蔣文豐、林凱健、陳義和、張清林

大腸癌是全球發病率最高的三大癌症之一。大腸鏡檢查被認為是診斷大腸息肉和腫瘤的金標準，可惜這種方法成本高，屬侵入性檢查和勞動密集型，所以被認為不適合作全民篩查的工具。其他替代大腸鏡檢查的方案包括愈創木脂和免疫化學大便隱血測試、電腦斷層結腸成像、結腸膠囊內視鏡檢查、乙狀結腸內視鏡檢查和雙對比鋇劑灌腸。本文綜述了這些替代方案的程序、試驗特點及可能的影響。要開展無症狀全民大腸癌篩查，似乎免疫化學大便隱血測試最為適合，其次為乙狀結腸內視鏡檢查。至於電腦斷層結腸成像和結腸膠囊內鏡檢查方面，則須搜集更多有關其作為篩檢工具的證據。

performing iFOBT at 1-, 2-, or 3-year intervals did not yield significantly different results in terms of advanced adenoma detection, but compliance decreased with frequent screening.²⁴

The stability of the iFOBT kit is temperature-dependent, making results vulnerable to changes in environmental temperature and the sample return time.²⁰ In moderate climates, the sample return time should not exceed 7 days.²⁵ Manufacturers are developing buffer solutions to overcome this problem.¹⁵

A potential disadvantage of iFOBT is its decreased sensitivity to proximal colonic lesions. A German study showed a sensitivity of 33% and 20% for left- and right-sided lesions, respectively. Nonetheless the results were statistically insignificant,²⁶ and were contradictory to another Dutch trial.²⁷

The positivity rate of iFOBT ranges from 5.5% to 11.0%.^{12,13,17,19,28,29} The sensitivity and specificity for CRC ranges from 53.3% to 94.1% and 87.5% to 96.9%, respectively.^{18,28,30,31} The PPV ranges from 5.2% to 12.8% at a cut-off value of 75 ng/mL.^{12,13,17-19,28-32} The NNScreen and NNScope ranges from 213 to 936 and

TABLE 1. Summary of four randomised controlled trials comparing screening with guaiac faecal occult blood testing with no screening* 7-10

Study	Year	Screening	Control	Follow-up duration (years)	Age at recruitment (years)	Reduction in CRC mortality (%)	Relative reduction in CRC mortality (95% CI)
Shaukat et al ⁷	2013	15 570 (annual); 15 587 (biennial)	15 394	30	50-80	33 20	0.68 (0.56-0.82) 0.78 (0.65-0.93)
Scholefield et al ⁸	2012	76 056	75 919	0.0-28.4	45-74	12†	0.88 (0.79-0.98)†
Lindholm et al ⁹	2008	34 144	34 164	11.3-19.5	60-64	16	0.84 (0.71-0.99)‡
Kronborg et al ¹⁰	2004	30 967	30 966	17	45-75	17	0.84 (0.73-0.96)

Abbreviations: CI = confidence interval; CRC = colorectal cancer

* Intention-to-treat analysis

† Calculation based on the first 12 years of study

‡ Odds ratio used in original article, relative risk calculated for representation here

TABLE 2. Studies showing performance of iFOBT, with or without comparison with gFOBT^{12,13,17-19,28-32}

Study	Country	Year	Screening tests*	Total No.	Age (years)	Sensitivity (%) (95% CI)	PPV for CRC (%) [95%CI]	NNScope (95%CI)	NNScreen (95%CI)
Allison et al ^{28†}	United States	2007	gFOBT2 iFOBT7	N/A	≥50	64.3 (35.6-86.0) 81.8 (47.8-96.8)	1.5 (0.8-3.0) 5.2 (2.6-10.0)	N/A	528.1 672.2
Levi et al ¹⁸	Israel	2007	iFOBT2	1859	N/A	88.2 (72.9-100)‡ 94.1 (82.9-100)§	12.9‡ 11.9§	N/A	N/A
van Rossum et al ¹³	The Netherlands	2008	gFOBT1 iFOBT2	10 322 10 301	50-75	N/A	10.7 (4.7-16.6) 8.6 (5.3-11.9)	9.4 11.7	430.1 936.5
Hol et al ¹²	The Netherlands	2009	gFOBT1 iFOBT2	4843 4796	50-74	N/A	10.0 (4.0-20.0) 10.0 (6.0-17.0)	10.3 9.8	392.0 213.0
Fu et al ¹⁹	Singapore	2009	iFOBT2	751	40-85	78.8	5.3	17.3	250.3
Park et al ³¹	Korea	2010	gFOBT1 iFOBT2	N/A	50-75	30.8 (9.1-61.4) 92.3 (64.0-99.8)	6.7 (1.8-15.9) 12.8 (6.6-21.7)	N/A	N/A
Faivre et al ³²	France	2012	gFOBT1 iFOBT2 iFOBT5 iFOBT6	85 149 32 215 19 244 33 690	50-74	2.1 (1.6-2.8)¶ 1.7 (1.3-2.1) 1.8 (1.3-2.3)	5.2-6.4 5.6 (4.3-6.9) 3.9 (2.9-4.9) 5.7 (3.9-7.1)	12.8 (10.8-15.9) 16.6 (13.9-20.7) 12.7 (10.3-16.6)	366 (303-455) 354 (286-435) 296 (238-385)
Tan et al ¹⁷	Singapore	2013	iFOBT1	20 989	≥50	N/A	6.7	15.0	636.0
Brenner and Tao ³⁰	Germany	2013	gFOBT1 iFOBT2 iFOBT3 iFOBT4	N/A	50-79	33.3 73.3 60.0 53.3	4.5 10.0 8.1 7.3	N/A	N/A
Raginel et al ²⁹	France	2013	gFOBT1 iFOBT2 iFOBT6	N/A	50-74	N/A	6.9 6.2 6.5	14.6 16.2 15.1	1041.9 549.9 449.9

Abbreviations: CI = confidence interval; CRC = colorectal cancer; gFOBT = guaiac faecal occult blood testing; iFOBT = immunohistochemical faecal occult blood testing; N/A = not available; NNScope = the number of colonoscopies needed to diagnose an advanced adenoma after screening revealed a likely significant lesion; NNScreen = the number of average-risk individuals needed to recruit in a screening programme to detect one advanced adenoma; PPV = positive predictive value

* gFOBT1 = Hemoccult II; gFOBT2 = Hemoccult Sensa; iFOBT1 = OC-Light; iFOBT2 = OC-SENSOR; iFOBT3 = RIDASCREEN Haemoglobin; iFOBT4 = RIDASCREEN Haemo-/Haptoglobin Complex; iFOBT5 = FOB-Gold; iFOBT6 = Magstream; iFOBT7 = FlexSure OBT

† Studied distal colorectal cancer only

‡ Cut-off value at 100 ng/mL

§ Cut-off value at 75 ng/mL

¶ Sensitivity ratio (ratio of true positives with iFOBT to that with gFOBT) was estimated as sensitivities could not be directly calculated

9.8 to 17.3, respectively.^{12,13,17,19,28-30,32} These results are summarised in Table 2. For advanced adenoma, the sensitivity and specificity ranges from 33.9% to 41.3% and 91.4% to 97.3%, respectively.^{18,28,31} The PPV ranges from 49.0% to 51.8%.^{12,13} The NNScope and NNScreen ranges from 2.2 to 2.4 and 88.0 to 135.6, respectively (single sample).²⁹

Compared with gFOBT, studies in the literature showed superior results for iFOBT that generally had a higher positivity rate, often 2 times higher than that of gFOBT.^{13,28} The detection rate for CRC in a study by Faivre et al³² was 1.6 to 2.1 times higher than in gFOBT. This was echoed by another large-scale RCT which showed a significantly higher detection rate using iFOBT.¹³ Studies showed the detection rate for advanced adenoma using iFOBT to be at least double that of gFOBT.^{12,29} In the study by Faivre et al,³² iFOBT was 1.7 to 2.1 times more sensitive than gFOBT for CRC.³² A study by Brenner and Tao³⁰ showed significantly higher PPV for iFOBTs than

gFOBTs (7.3%-10.0% vs 4.5%). In two comparative studies, the NNScreen of iFOBT was about half that of gFOBT^{29,32}; iFOBT also had a 13.0% to 15.0% higher participation rate than gFOBT.^{13,15,16,20,33}

The iFOBT is more costly than its guaiac-based counterpart,²⁰ but modelling studies showed that it is more cost-effective.³⁴⁻³⁷ This is largely explained by the higher participation rate, detection rate, sensitivity and PPV, and with lower NNScope and NNScreen. There is a general consensus that it should replace gFOBT.^{16,20,38}

Computed tomographic colonography

The CTC was first described in 1994.³⁹ It provides a non-invasive structural assessment of the colon. Compared with conventional colonoscopy, CTC is sedation-free and has an extremely low risk of bowel perforation (0.005%-0.059%).^{40,41} Furthermore,

assessment of the extra-colonic organs can be performed at the same time.⁴² A lower volume bowel preparation may be used⁴³ and the radiation risk is negligible.⁴¹ Its main disadvantage is that biopsy is not possible, and the patient may require a second procedure with another bowel preparation, thus imposing additional costs and discomfort to the patient. Its role in CRC screening remains debatable. The American Cancer Society supports screening with CTC every 5 years.⁴⁴ Other guidelines including the National Institutes of Health Asia Pacific Consensus Recommendations do not support its use, however, stating its lack of evidence as a screening technique in an average-risk population.^{45,46}

Studies of CTC in the literature use detection of polyps in general as the end-point. Data for detection of invasive carcinoma as well as reduction in CRC mortality were not available. Different studies use either 'per patient' or 'per polyp' for analysis. Two large US trials supported CTC as a screening tool in asymptomatic average-risk populations.^{47,48} Per-patient analyses demonstrated a sensitivity of 78.0% to 93.8%, and specificity of 79.6% to 96.0%, respectively.^{47,48} Meta-analyses in 2011 and 2014 reviewed 15 trials,^{49,50} including the two aforementioned studies. All trials focused on a population aged over 50 years with average risk. Martín-López et al⁴⁹ showed an overall per-patient sensitivity and specificity for CTC of 66.8% and 80.3%, which was lower than that of colonoscopy of 92.5% and 73.2%, respectively. The sensitivity and specificity were higher for larger polyps. For polyps larger than 1 cm, the sensitivity was 91.2% and specificity 87.3%. Another meta-analysis reported sensitivities for ≥ 6 -mm and ≥ 10 -mm polyps as 75.9% and 83.3% and specificities as 94.6% and 98.7%, respectively.⁵⁰

Estimation of the cost-effectiveness remains complicated. Based on a systematic review of 16 studies,⁵¹ the cost-effectiveness of CTC remains controversial. There is generally a stronger preference for CTC over colonoscopy in asymptomatic individuals,⁵² although some may hold an opposite opinion due to more pain and discomfort in CTC.⁵³ The use of 'low-prep' or laxative-free CTC is being further investigated.⁴³

The CTC can detect asymptomatic polyps and has the potential to prevent them from progressing to advanced adenoma and CRC. These polyps may not be detected by gFOBT or iFOBT until they result in microscopic haemorrhage in the lower GI tract. This is an advantage of CTC compared with gFOBT and iFOBT. The role of CTC in reducing CRC mortality remains uncertain, however.

Colon capsule endoscopy

The CCE makes use of a double-headed capsule with a wide viewing angle, visualising the colon beyond the haustral folds.⁵⁴ Its sensitivity and specificity

for significant polyps has been reported to be 83% and 89%, respectively.⁵⁵⁻⁵⁷ The European Society of Gastrointestinal Endoscopy recommends CCE as an alternative screening method for average-risk individuals.⁵⁸ In February 2014, it also received the US Food and Drug Administration clearance for use in patients following incomplete colonoscopy. It is also proven to be beneficial when the patient is unwilling or is unable to undergo colonoscopy.^{59,60} With its presumed increased uptake, it is a promising new CRC screening modality.⁶¹ The newest generation of CCE has improved resolution by adapting its frame rate to the speed of capsule movement. Some newer capsules also have four cameras to provide a 360-degree view.⁶²

Despite its promising role in screening, some disadvantages of CCE have limited its use thus far. Strict bowel preparation, diet restrictions, and use of suppositories and prokinetics may be needed to ensure a smooth and quick journey of the capsule through the bowel, while minimising the interference of debris when identifying lesions.⁶³ Potential complications include capsule impaction and retention (1.4%⁶⁴) that may require endoscopic or surgical removal. It is also not recommended in pregnancy or with implanted electromedical devices such as pacemakers.⁶² The cost of CCE is much higher than that of colonoscopy,⁶⁵ and includes the reading of the captured video footage. There is also no current evidence to prove the mortality benefit of CCE use in CRC.

Flexible sigmoidoscopy

The FS examines the distal 40 to 60 cm of the lower GI tract. Full colonoscopy can be performed when there are positive findings. Compared with colonoscopy, it requires a simpler bowel preparation and dietary restriction is not necessary.⁶⁶

In two large-scale RCTs that involved 170 432 and 55 736 individuals, in PP analysis, there was a 43.0% reduction in CRC mortality and improved hazard ratio of 0.41.^{67,68} This was echoed by another RCT that involved 77 445 patients and showed a 21% reduction in the incidence of both proximal and distal cancer and a 50% reduction in mortality from distal cancer.⁶⁹ The PPV was 91.9% for any adenoma.⁷⁰ The positivity rate for adenoma was 17.3%.⁷¹ Most studies were in individuals aged ≥ 50 ⁷⁰⁻⁷² or ≥ 55 years.^{68,69,73}

The sensitivity of FS depends on the adequacy of mucosal inspection and is operator-dependent.⁷³ Studies have shown inadequate screening in up to 91.7% of cases, ie < 50 cm depth of insertion.⁷³ The technique had relatively low and fluctuating participation rates (20.9%-63.0%).^{70,71} A 35.3% decrease in adherence from baseline to subsequent study was observed.⁶⁹

The impact of FS as a screening tool is well established in the literature and accepted in various

screening protocols.^{44,46} This technique should be included as an alternative choice for a population-wide screening programme, and the shortage of endoscopists could be partially addressed by training specialised nurses in the procedure.⁷⁴

Combining flexible sigmoidoscopy with guaiac and immunohistochemical faecal occult blood testing

Flexible sigmoidoscopy cannot replace the role of colonoscopy in individuals with a positive faecal occult blood test.⁷² In a non-randomised trial, the detection rate of combined gFOBT and FS for cancer was higher than that of gFOBT alone (1.5 vs 0.7 per 1000), but was not superior to FS alone (1.5 vs 5.2 per 1000).⁷⁰ Results were similar for advanced neoplasia.

Double-contrast barium enema

The DCBE involves an X-ray study of the colon and rectum following injection of air and barium transrectally. Once regarded as a routine screening tool, its role has diminished since the introduction of other screening modalities. While it was the safest screening method next to FOBT with a perforation rate of 1 in 25 000,⁷⁵ the sensitivity for polyps of ≥ 10 mm was only 48%, rendering it suboptimal for screening.^{76,77}

Combining double-contrast barium enema with flexible sigmoidoscopy

When DCBE was combined with FS, they had the same sensitivity for cancer as colonoscopy (96.7%).⁷⁸ Two RCTs in the 1990s reported a lower detection rate for small polyps for FS plus DCBE when compared with colonoscopy.^{79,80} Nonetheless the detection rate for cancers and large polyps was comparable.⁷⁹ Sensitivity analyses in both studies revealed that in screening, FS plus DCBE was less cost-effective than colonoscopy.

Current guidelines

The Asia Pacific Consensus Recommendations in 2015 suggested the use of iFOBT over gFOBT, and FS and colonoscopy were deemed effective.⁴⁶ On the contrary, CTC and CCE were not recommended for screening. In the US, surveillance programme guidelines from the American Cancer Society provided two sets of test options for asymptomatic adults aged ≥ 50 years.⁴⁴ For adenomatous polyps and cancer, FS, DCBE, or CTC every 5 years, or colonoscopy every 10 years was recommended. For cancer alone, annual gFOBT or iFOBT testing was recommended. The American College of Gastroenterology supported replacement of gFOBT by iFOBT as a first-line screening test.⁸¹ The National Health Service in the UK recommends

screening for average-risk men and women aged 60 to 74 years with FOBT every 2 years.⁸² The European Union did not offer a comprehensive system, with a recommendation of FOBT for men and women aged 50 to 74 years.⁸³ The Australian government encouraged biennial iFOBT for an asymptomatic population aged >50 years.⁸⁴

There is no formal consensus on a CRC screening programme in Hong Kong. The Hong Kong Cancer Fund, a cancer support organisation, recommends screening of the average-risk population aged ≥ 50 years, with either FOBT every year, FS or DCBE every 5 years, or colonoscopy every 10 years.⁸⁵

Discussion

Colonoscopy remains the gold standard diagnostic tool for CRC, but its costs, discomfort, inconvenience, and potential complications render it impractical as the first-line investigation in a population-wide CRC screening programme for average-risk individuals. Multiple alternative tools have since been developed, aimed at minimising discomfort and inconvenience and thus achieving better compliance, while at the same time not jeopardising the screening effectiveness. While it is not possible for these tools to replace colonoscopy for diagnosis, they may assume an essential role in a screening programme as an index investigation for risk stratification, thus selecting patients to undergo further diagnostic colonoscopy.

These screening modalities differ in their development. Both gFOBT and FS are time-honoured, heavily researched, and proven to reduce CRC mortality. Large amounts of research data are emerging in support of newer options such as iFOBT and CTC. While comparison of gFOBT and iFOBT is easily achievable, direct comparison of CTC and iFOBT is more difficult as there are different 'performance' parameters.

The technique iFOBT is evolved from gFOBT and shares a similar mechanism. While gFOBT has been well proven by long-duration RCTs to reduce CRC mortality, it has been postulated that iFOBT may achieve the same effect. For a population-wide screening programme to be successful, the test has to be acceptable to asymptomatic individuals. This eventually determines the penetration and compliance with the programme. Compared with gFOBT, iFOBT undeniably has a higher participation rate,^{13,20,33} and even more so compared with FS.^{70,71} In a population-wide screening programme with iFOBT, implementation could be achieved in a relatively short period of time as it could be performed by primary care physicians and nurses. Installation of sophisticated hardware is not required. Given a positivity rate of 5.5% to 11.0%,^{12,13,17,19,28,29} however, it would have a significant impact on health care

services. A major increase in the number of referrals for colonoscopy would be anticipated and thus require a corresponding increase in the availability of endoscopy centres and endoscopists.

Test characteristics are not the only factor that dictates the success of a screening programme; compliance plays a crucial role. Studies have shown that those who communicate well with their health care providers are more likely to adhere to a screening programme.⁸⁶ When implementing a population-wide programme, recruiting primary care physicians to promote CRC screening and perform office-based iFOBT would be logical and is feasible.

Conclusion

Each CRC screening modality has its own niche, providing unique prognostic benefits but with their own shortcomings. Based on the available evidence to date, feasibility, and participant acceptance, iFOBT appears to be the most suitable CRC index screening tool for the average-risk population, with FS as an alternative.

References

- Bernard WS, Christopher PW. World Cancer Report 2014: Colorectal cancer. Lyon, France: International Agency for Research on Cancer, WHO; 2014: 392-402.
- Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007;50:113-30.
- Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988;319:525-32.
- Snover DC. Update on the serrated pathway to colorectal carcinoma. *Hum Pathol* 2011;42:1-10.
- Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. *Gut* 2007;56:1585-9.
- Waldmann E, Regula J, Ferlitsch M. How can screening colonoscopy be optimized? *Dig Dis* 2015;33:19-27.
- Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. *N Engl J Med* 2013;369:1106-14.
- Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut* 2012;61:1036-40.
- Lindholm E, Brevinge H, Haglund E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg* 2008;95:1029-36.
- Kronborg O, Jørgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol* 2004;39:846-51.
- Parra-Blanco A, Gimeno-García AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. *J Gastroenterol* 2010;45:703-12.
- Hol L, Wilschut JA, van Ballegooijen M, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. *Br J Cancer* 2009;100:1103-10.
- van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008;135:82-90.
- Dancourt V, Lejeune C, Lepage C, Gailliard MC, Meny B, Faivre J. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. *Eur J Cancer* 2008;44:2254-8.
- Duffy MJ, van Rossum LG, van Turenhout ST, et al. Use of faecal markers in screening for colorectal neoplasia: a European group on tumor markers position paper. *Int J Cancer* 2011;128:3-11.
- Leggett BA, Hewett DG. Colorectal cancer screening. *Intern Med J* 2015;45:6-15.
- Tan WS, Tang CL, Koo WH. Opportunistic screening for colorectal neoplasia in Singapore using faecal immunochemical occult blood test. *Singapore Med J* 2013;54:220-3.
- Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Ann Intern Med* 2007;146:244-55.
- Fu WP, Kam MH, Ling WM, Ong SF, Suzannah N, Eu KW. Screening for colorectal cancer using a quantitative immunochemical faecal occult blood test: a feasibility study in an Asian population. *Tech Coloproctol* 2009;13:225-30.
- Kuipers EJ, Rösch T, Bretthauer M. Colorectal cancer screening—optimizing current strategies and new directions. *Nat Rev Clin Oncol* 2013;10:130-42.
- Guittet L, Bouvier V, Mariotte N, et al. Performance of immunochemical faecal occult blood test in colorectal cancer screening in average-risk population according to positivity threshold and number of samples. *Int J Cancer* 2009;125:1127-33.
- Grazzini G, Visioli CB, Zorzi M, et al. Immunochemical faecal occult blood test: number of samples and positivity cutoff. What is the best strategy for colorectal cancer screening? *Br J Cancer* 2009;100:259-65.
- Faivre J, Dancourt V, Manfredi S, et al. Positivity rates and performances of immunochemical faecal occult blood tests at different cut-off levels within a colorectal cancer screening programme. *Dig Liver Dis* 2012;44:700-4.
- van Roon AH, Goede SL, van Ballegooijen M, et al. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. *Gut* 2013;62:409-15.
- van Roon AH, Hol L, van Vuuren AJ, et al. Are fecal immunochemical test characteristics influenced by sample return time? A population-based colorectal cancer screening trial. *Am J Gastroenterol* 2012;107:99-107.
- Haug U, Kuntz KM, Knudsen AB, Hundt S, Brenner H. Sensitivity of immunochemical faecal occult blood testing for detecting left- vs right-sided colorectal neoplasia. *Br J Cancer* 2011;104:1779-85.
- de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. *Am J Gastroenterol* 2012;107:1570-8.
- Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests:

- Update on performance characteristics. *J Natl Cancer Inst* 2007;99:1462-70.
29. Raginel T, Puvinel J, Ferrand O, et al. A population-based comparison of immunochemical fecal occult blood tests for colorectal cancer screening. *Gastroenterology* 2013;144:918-25.
 30. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. *Eur J Cancer* 2013;49:3049-54.
 31. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol* 2010;105:2017-25.
 32. Faivre J, Dancourt V, Denis B, et al. Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer. *Eur J Cancer* 2012;48:2969-76.
 33. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2010;59:62-8.
 34. Berchi C, Bouvier V, Réaud JM, Launoy G. Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France. *Health Econ* 2004;13:227-38.
 35. Berchi C, Guittet L, Bouvier V, Launoy G. Cost-effectiveness analysis of the optimal threshold of an automated immunochemical test for colorectal cancer screening: performances of immunochemical colorectal cancer screening. *Int J Technol Assess Health Care* 2010;26:48-53.
 36. Grazzini G, Ciatto S, Cislighi C, et al. Cost evaluation in a colorectal cancer screening programme by faecal occult blood test in the District of Florence. *J Med Screen* 2008;15:175-81.
 37. van Rossum LG, van Rijn AE, Verbeek AL, et al. Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis. *Int J Cancer* 2011;128:1908-17.
 38. Lieberman D. Colorectal cancer screening: practice guidelines. *Dig Dis* 2012;30 Suppl 2:34-8.
 39. Vining DJ, Shifrin RY, Grishaw EK, Liu K, Gelfand DW. Virtual colonoscopy. *Radiology* 1994;193(P):446.
 40. Sosna J, Blachar A, Amitai M, et al. Colonic perforation at CT colonography: assessment of risk in a multicenter large cohort. *Radiology* 2006;239:457-63.
 41. Berrington de Gonzalez A, Kim KP, Yee J. CT colonography: perforation rates and potential radiation risks. *Gastrointest Endosc Clin N Am* 2010;20:279-91.
 42. Pickhardt PJ, Hanson ME, Vanness DJ, et al. Unsuspected extracolonic findings at screening CT colonography: clinical and economic impact. *Radiology* 2008;249:151-9.
 43. Zalis ME, Blake MA, Cai W, et al. Diagnostic accuracy of laxative-free computed tomographic colonography for detection of adenomatous polyps in asymptomatic adults, a prospective evaluation. *Ann Intern Med* 2012;156:692-702.
 44. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570-95.
 45. Steinwachs D, Allen JD, Barlow WE, et al. NIH state-of-the-science conference statement: Enhancing use and quality of colorectal cancer screening. *NIH Consens State Sci Statements* 2010;27:1-31.
 46. Sung JJ, Ng SC, Chan FK, et al. An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. *Gut* 2015;64:121-32.
 47. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003;349:2191-200.
 48. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008;359:1207-17.
 49. Martín-López JE, Beltrán-Calvo C, Rodríguez-López R, Molina-López T. Comparison of the accuracy of CT colonography and colonoscopy in the diagnosis of colorectal cancer. *Colorectal Dis* 2014;16:O82-9.
 50. de Haan MC, van Gelder RE, Graser A, Bipat S, Stoker J. Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. *Eur Radiol* 2011;21:1747-63.
 51. Hanly P, Skally M, Fenlon H, Sharp L. Cost-effectiveness of computed tomography colonography in colorectal cancer screening: a systematic review. *Int J Technol Assess Health Care* 2012;28:415-23.
 52. Lin OS, Kozarek RA, Gluck M, et al. Preference for colonoscopy versus computerized tomographic colonography: a systematic review and meta-analysis of observational studies. *J Gen Intern Med* 2012;27:1349-60.
 53. Ou G, Rosenfeld G, Fu YT, et al. Patient satisfaction and preferences: colonoscopy or computed tomography colonography for colorectal cancer screening. *Gastrointest Endosc* 2012;75 Suppl:AB140.
 54. Hale MF, Sidhu R, McAlindon ME. Capsule endoscopy: current practice and future directions. *World J Gastroenterol* 2014;20:7752-9.
 55. Eliakim R, Yassin K, Niv Y, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009;41:1026-31.
 56. Spada C, Hassan C, Munoz-Navas M, et al. Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011;74:581-9.e1.
 57. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of PillCam COLON 2 for detecting subjects with adenomas ≥ 6 mm. *Gastrointest Endosc* 2013;77 Suppl 1:AB29.
 58. Spada C, Hassan C, Galmiche JP, et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2012;44:527-36.
 59. Pioche M, de Leusse A, Filoche B, et al. Prospective multicenter evaluation of colon capsule examination indicated by colonoscopy failure or anesthesia contraindication. *Endoscopy* 2012;44:911-6.
 60. Negreanu L, Babiuc R, Bengus A, Sadagurschi R. PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy. *World J Gastrointest Endosc* 2013;5:559-67.
 61. Sieg A, Friedrich K, Sieg U. Is PillCam COLON capsule endoscopy ready for colorectal cancer screening? A prospective feasibility study in a community gastroenterology practice. *Am J Gastroenterol*

- 2009;104:848-54.
62. Bouchard S, Ibrahim M, van Gossum A. Video capsule endoscopy: perspectives of a revolutionary technique. *World J Gastroenterol* 2014;20:17330-44.
 63. Spada C, Barbaro F, Andrisani G, et al. Colon capsule endoscopy: What we know and what we would like to know. *World J Gastroenterol* 2014;20:16948-55.
 64. Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 2010;71:280-6.
 65. Triantafyllou K, Beintaris I, Dimitriadis GD. Is there a role for colon capsule endoscopy beyond colorectal cancer screening? A literature review. *World J Gastroenterol* 2014;20:13006-14.
 66. Regge D, Iussich G, Senore C, et al. Population screening for colorectal cancer by flexible sigmoidoscopy or CT colonography: study protocol for a multicenter randomized trial. *Trials* 2014;15:97.
 67. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010;375:1624-33.
 68. Hoff G, Grotmol T, Skovlund E, Bretthauer M; Norwegian Colorectal Cancer Prevention Study Group. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. *BMJ* 2009;338:b1846.
 69. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med* 2012;366:2345-57.
 70. Denis B, Gendre I, Aman F, Ribstein F, Maurin P, Perrin P. Colorectal cancer screening with the addition of flexible sigmoidoscopy to guaiac-based faecal occult blood testing: A French population-based controlled study (Wintzenheim trial). *Eur J Cancer* 2009;45:3282-90.
 71. Holme Ø, Løberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA* 2014;312:606-15.
 72. Mansouri D, McMillan DC, Roxburgh CS, Moug SJ, Crighton EM, Horgan PG. Flexible sigmoidoscopy following a positive faecal occult blood test within a bowel screening programme may reduce the detection of neoplasia. *Colorectal Dis* 2013;15:1375-81.
 73. Laiyemo AO, Doubeni C, Pinsky PF, et al. Factors associated with inadequate colorectal cancer screening with flexible sigmoidoscopy. *Cancer Epidemiol* 2012;36:395-9.
 74. Shum NF, Lui YL, Choi HK, Lau SC, Ho JW. A comprehensive training programme for nurse endoscopist performing flexible sigmoidoscopy in Hong Kong. *J Clin Nurs* 2010;19:1891-6.
 75. Blakeborough A, Sheridan MB, Chapman AH. Complications of barium enema examinations: A survey of UK consultant radiologists 1992 to 1994. *Clin Radiol* 1997;52:142-8.
 76. Winawer SJ, Stewart ET, Zauber AG, et al. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N Engl J Med* 2000;342:1766-72.
 77. Canon CL. Is there still a role for double-contrast barium enema examination? *Clin Gastroenterol Hepatol* 2008;6:389-92.
 78. Robinson MH, Hardcastle JD, Moss SM, et al. The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. *Gut* 1999;45:588-92.
 79. Rex DK, Weddle RA, Lehman GA, et al. Flexible sigmoidoscopy plus air contrast barium enema versus colonoscopy for suspected lower gastrointestinal bleeding. *Gastroenterology* 1990;98:855-61.
 80. Rex DK, Mark D, Clarke B, Lappas JC, Lehman GA. Flexible sigmoidoscopy plus air-contrast barium enema versus colonoscopy for evaluation of symptomatic patients without evidence of bleeding. *Gastrointest Endosc* 1995;42:132-8.
 81. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM; American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 2009;104:739-50.
 82. Bowel cancer—screening. Available from: <http://www.nhs.uk/Conditions/Cancer-of-the-colon-rectum-or-bowel/Pages/Screeningforbowelcancer.aspx>. Accessed Dec 2015.
 83. von Karsa L, Patnick J, Segnan N. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition—Executive summary. *Endoscopy* 2012;44 Suppl 3:SE1-8.
 84. Thomas R, Michael S, Finlay M, et al. Australian Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. Natl Heal Med Res Counc Aust Gov; 2005.
 85. Early detection and prevention. Available from: <http://www.cancer-fund.org/colorectal/html/eng/detection.html>. Accessed Dec 2015.
 86. Francisco D, Rankin L, Kim SC. Adherence to colorectal cancer and polyps screening recommendations among filipino-americans. *Gastroenterol Nurs* 2014;37:384-90.