Point-of-Care Faecal Occult Blood Testing

Horizon Scan Report 0035
February 2014

Clinical Question:

In patients at risk for colorectal cancer, what is the comparative accuracy and utility of home one-step faecal immunochemical testing?

Background, Current Practice and Advantages over Existing Technology:

Early detection of low-grade colorectal cancer (CRC) increases the likelihood of survival (1, 2). Depending on the patient's age, NICE recommend two week-wait referral for persistent rectal bleeding, a persistent change in bowel habit, the presence of a palpable right lower abdominal or a rectal mass, and unexplained iron deficiency anaemia (3). NICE do not recommend the use of faecal occult blood testing (FOBt) for the assessment of patients with symptoms suggestive of gastrointestinal disease, but there are many home testing kits available on the UK market despite media caution regarding their safety (4-6).

However evidence shows the diagnostic yield from symptoms and signs alone is limited. Three recent systematic reviews have evaluated the use of symptoms in the diagnosis of CRC (1, 7, 8). Jellema et al. included 47 cohort studies of patients with abdominal symptoms showing individual symptoms to have poor diagnostic value, that weight-loss had most diagnostic value (Sensitivity 20%, Specificity 89%), that iron deficiency anaemia performed poorly (Sensitivity 13%, Specificity 92%), and that combining symptoms and signs improves sensitivity (91%) at the expense of specificity (42%) (1). However, these studies were generally performed in secondary care, five at the interface between primary and secondary care, and only nine in a primary care setting with a prevalence of 3-15% for CRC. Sufficient data for primary vs. secondary care comparisons (sensitivity range, specificity range) was available for only the symptoms of weight loss (13-44 vs. 17-30%, 85-94 vs. 84-93%), abdominal pain (0-40% vs. 0-73%, 40-91% vs. 19-84%), and change in bowel habit (10-100% vs. 6-86%, 55-93 vs. 28-94%), adding little to explanations of heterogeneity between studies. Furthermore, seven of the studies from primary care selected a high risk population by using rectal bleeding as an inclusion criterion (1).

Astin et al. retrieved 23 primary care studies estimating positive predictive values (PPV) of 8.1% (95% CI 6-11) for rectal bleeding in those >50yrs from 13 studies, 3.3% (95% CI 0.7-16) for abdominal pain from three studies, and 9.7% (95% CI 3.5-27) for anaemia from four studies. They reported the positive likelihood ratio (PLR) of 1.9% (95% CI 1.3-2.8) for rectal bleeding and weight loss combined, and 1.8% (95% CI 1.3-2.5) rectal bleeding and a change in bowel habit combined demonstrating higher risk for symptom combinations. Despite making recommendations that general practitioners should investigate rectal bleeding, anaemia, and combinations of lower abdominal symptoms, they acknowledged the considerable limitations of between study heterogeneity, small sample sizes, and the relatively few studies reporting individual symptoms (7). Adelstein et al (2011) included 62 diagnostic accuracy studies mainly from endoscopy units or radiology centres, categorising together data from 19 studies from the general practice, screening and community settings. They reported overall poor study quality with inconsistency in methods of symptom elicitation and interpretation, recommending that colonoscopy is performed only in people with weight loss (Sensitivity 20%, Specificity 92%) or rectal bleeding (Sensitivity 46%, Specificity 75%) (8).

Risk assessment tools assist diagnosis, but currently rely on retrospective routinely entered data requiring validation in larger cohorts (9), and a diagnostic algorithm detects the 10% of the general population within which it is most likely that 70% of new CRC cases will be diagnosed within 2 years (10).

Screening detects CRC at earlier grades decreasing the number of cases presenting with symptoms. One study showed asymptomatic screening detected CRC is four times more likely to be diagnosed as low grade disease (Dukes A) (p<0.001) and significantly fewer as high grade (Dukes D) compared to symptomatic patients referred via the 2-week-wait pathway or to rectal bleeding outpatient clinics (11, 12). There is however international discord on the optimal approach to bowel cancer screening and consequently variation in the method used (13). The NHS Bowel Cancer Screening Programme (BCSP) screens asymptomatic individuals every two years between 60-74yrs using a card-based (six samples from three bowel motions) Guaiac-based Faecal Occult Blood Test (gFOB). The kit is returned by freepost within 14 days and analysed in a central laboratory. The patient has no contact with a health professional unless they have an abnormal gFOB result, in which case they are offered an appointment with a screening nurse to decide on the most appropriate next steps. Uptake of the BCSP screening is low (57%) compared to other screening programmes (14) such as the NHS cervical and breast screening programmes (15).

Socioeconomic status, age, gender, and health literacy are known predictors of screening uptake, but dislike of the FOBt is a significantly more commonly cited barrier to uptake than other screening modalities (16-18). Focus groups with 39 participants from diverse backgrounds found barriers to be fear of the test, fear of abnormal findings, no doctor recommendation, prohibitive cost, and a misunderstanding that asymptomatic patients do not need screening (19). GP recommendation was found to be the most common reason for uptake. GP involvement in the screening process is known

to address the socioeconomic inequalities as the more deprived less health-literate patients rely more upon their GP to inform their decision to screen (17, 19).

There have been a number of attempts to increase screening uptake, including: advance notification letters (20-22), GP involvement in and endorsement of screening compared to hospital coordinated (RR 3.4 95% CI 3.13-3.70) (23, 24), 46.7% of patients would prefer to return their sample to their GP (16). A letter of endorsement signed by the patient's own GP together with a how-to-do-it information leaflet sent with the BCSP kit led to a relative 20% (absolute 10%) increase in participation rates (25), electronic GP reminders to discuss screening have shown promise for frequent attenders (22), offering home FOBt during community influenza vaccination campaigns can increase uptake (OR 2.22 95% CI 1.24-3.95) (26), and offering an alternative secondary test to non-participants of the first round of screening can improve participation (27).

As there are a growing number of home point-of-care FOBt kits on the market, they could be used to address test-related barriers by improving acceptability and diagnostic accuracy, in symptomatic and asymptomatic patients.

Details of Technology:

Compared to colonoscopy, the reference standard for the detection of CRC, FOBt is non-invasive, inexpensive, and can be performed at home. FOBts are designed to detect blood mixed into the stools from large colorectal polyps and CRC which have a tendency to bleed. There are two main types; Guaiac FOBt (gFOB), and Faecal Immunochemical Testing (FIT). Newer tests attempt to detect DNA from the tumour cells in faeces, rather than blood (Faecal DNA testing).

Laboratory-based Guaiac FOB

Currently used by the NHS BCSP, gFOB detects the pseudo-peroxidase activity of haem or haemoglobin in the faeces. Test procedures vary between available kits, but to improve precision two samples are commonly smeared onto a test card from each of three consecutive motions. The cards are then sent to the laboratory where a hydrogen peroxide reagent is added to the sample to produce a change in colour signifying a positive test. To decrease the risk of false positive results, gFOB procedures recommend sampling from three consecutive stool samples. Most randomised controlled trial (RCT) evidence exists for the Hemoccult II test, but diagnostic test accuracy studies show other available gFOBs demonstrate similar accuracy (28, 29). False-positives can be caused by ingested haemoglobin from red meat, by some chemicals (plant peroxidases and vitamin C), and by bleeding from anywhere in the GI tract, leading to restrictions of diet and medication prior to sampling.

Laboratory-based Quantitative Faecal Immunochemical Tests

Newer faecal immunochemical tests (FIT) measure the globin component of human haemoglobin (HGP) meaning dietary restrictions are not required, they are also more specific to lower GI cancers as upper GI enzymes degrade HGP, they are less affected (and in some cases enhanced) by concomitant medication use, and consequently fewer stool samples are required. Quantitative and qualitative FITs exist. Laboratory based quantitative FITs allow thresholds to be selected for individual populations with automated interpretation allowing standardisation and removing inter-observer variation (28, 30).

Point-of-care Qualitative Faecal Immunochemical Tests

A proliferation of point-of-care qualitative FITs have emerged for use in a clinical setting or at home. A major advantage of the qualitative FITs is their easy one-stool-sample procedure sampling from multiple sites of a single stool, with immediate results using a pre-defined dichotomous threshold removing the necessity for costly laboratory equipment, (31). Like gFOB they run the risk of inter-observer variation, with the possibility of variable interpretation of borderline results. Table 1.shows the CE approved FIT kits currently sold in the UK, marketed as stand-alone home-test kits for use on a single stool sample with rapid results. The PRIMA home test is included as it is a stand-alone test that is repeated on three samples. We did not find FDA approval nor any studies evaluating the diagnostic accuracy of any of these kits.

Table 1: CE marked point of care faecal immunochemical test kits marketed for home use in the UK.

Kit	Manufacturer / Distributer.	Method	Hb threshold	Price
SELF-SURE™	Epitope Diagnostics Inc, San Diego, USA. (distributed by Personal Diagnostics, UK)	Plastic stool collection device stabs stool at "two or more sites", is then twisted into sealed sampling tube containing developing suspension and shaken. Test strip is screwed into other end of sealed sampling tube and result given.	Not specified	£11.99p
FOBCHECK©	NanoRepro, Marburg, Germany. Distributed through Amazon.co.uk	Plastic stool collection device stabs stool at "various locations", is then twisted into sealed sampling tube containing developing suspension and mixed. Top is unscrewed and 3 drops are dropped into the sample well of the test device and result given.	40 µg/l	£15.95p (2 kits)
Certain Bowel Health Test	KOROGLU MEDICAL DEVICES LTD, Turkey. Distributed through Amazon.co.uk	Sampling device incorporated into the lid of the developing solution bottle is used to stab stool at "three different locations" then is fastened and shaken. Tip of top is snapped off and 3-4 drops are dropped into the dropping hole of the test device and result given.	30 µg/l	£5.59p
SELFCheck home screening test: Bowel Health Kit	CARE Diagnostica Austria. Distributed by1st Health Products Ltd, UK via Amazon.co.uk	Sampling device incorporated into the lid of the developing solution bottle is used to stab stool taking "3-6 samples at different locations" then is fastened and shaken. Tip of top is snapped off and 2 drops are dropped into the dropping hole of the test cassette and result given in 5 minutes.	Not specified	£11.12p

BOWEL HOME TEST Kit	The Boots company PLC, Nottingham, England. Boots Pharmaceuticals.	Sampling device incorporated into the lid of the developing solution bottle is used to stab stool taking "3-6 samples at different locations " then is fastened and shaken. Tip of top is snapped off and 2 drops are dropped into the dropping hole of the test cassette and result given in 5 minutes.	Not specified	£12.25p
PRIMA® Home Test: Bowel Test – FOB.	HEALTHY EUROPE s.r.l. Milan Italy. Distributed through Amazon.co.uk	Unscrew the syringe cap and dip the stick about 2cm into the faeces at 3 separate locations, replace the collection stick to the collection device and shake well repeating this procedure three times on separate stools keeping the device in the fridge in between. Snap off the tip and drop 6 drops to the sample well and read the result after 10 minutes.	Not specified	£9.99p

Laboratory Based Faecal DNA tests

Faecal DNA testing is a comparatively novel rapidly developing technique showing great potential for CRC diagnosis and screening. Newer-generation tests detect hypermethylated genes found in CRC and precancerous lesions, including secreted frizzled related protein 2 (Sfrp2), septin 9 (SEPT9), vimentin, and bone morphogenetic protein 3 (BMP3) (32). DNA marker panels are reported to show sensitivities of 75%–91% for CRC and 44%– 85% for adenomas, with high specificities (82%–96%), with potential benefits over colonoscopy in detecting ascending colon lesions. However, at present larger studies are needed to validate findings and to optimise the faecal DNA test, cost is prohibitive exceeding that of all other screening modalities (FOBt, Flexible Sigmoidoscopy, colonoscopy), and there is no point of care test kits available (32, 33).

Patient Group and Use:

- Average-risk asymptomatic adult patients undergoing screening for bowel cancer, or patients presenting to their GP with symptoms suggestive of CRC.

Importance:

Colorectal cancer is the third most common cancer worldwide after lung and breast, incidence patterns are associated with family history and genetics, and variations in diet, deprivation, bodyweight, and physical activity. In the UK in 2010, colorectal cancer was the fourth most common cancer accounting for 40,695 new cases and 10% of cancer related deaths (Cancer Research UK). Whilst UK incidence has steadily increased since the 1970's, with the largest increases seen in the 60-79yr olds, mortality rates have slowly decreased. The lifetime risk of being diagnosed with bowel cancer is around 1 in 20 for women and 1 in 18 for men.

Previous Research:

Accuracy compared to existing technology

Symptomatic FOBt

For symptomatic patients Jellema et al reported the sensitivity of gFOB to range from 33-100% with specificity ranging from 72-94%. Two gFOB self-tests were included for use in symptomatic patients: the Coloscreen and EZ-Wipe tests both involved floating a reagent impregnated tissue atop the toilet water after passing a motion, on three consecutive days, with a change in tissue colour associated with a positive result. The sensitivities for these self-tests were low (33-57%) and were reported by the respective study authors to be too low for use in symptomatic patients (34-36).

Jellema et al reported that FIT showed promise as an easy-to-perform, well tolerated primary care based investigation for CRC (sensitivity 50-100%, specificity 71-93%), but noted great heterogeneity between studies and a lack of evidence on diagnostic accuracy from symptomatic primary care populations, calling for cohort studies investigating patients presenting with non-acute abdominal symptoms in primary care (1).

We found one study evaluating the use of a one-step FIT in primary care. Kaul et al performed a one-step qualitative FIT on 126 patients without overt rectal bleeding who were referred for urgent assessment for CRC, and reported that FIT had a sensitivity of 100% and specificity of 86.3% (confidence intervals not reported) for CRC suggesting potential value for FIT to triage referrals to secondary care (37). It is unclear whether this accuracy would remain if the test was used at home.

Asymptomatic qualitative FIT

We found no studies explicitly evaluating the accuracy of qualitative FIT screening conducted at home by patients. There is however data available for gFOB and quantitative FIT from a variety of settings (as later specified) from which comparative diagnostic accuracy can be inferred.

gFOB

A Cochrane systematic review has shown that biennial population screening with card-based postal laboratory-analysed gFOB can reduce colorectal mortality by 15% (RR 0.85, CI: 0.78-0.92) in people aged 45-74, and those that attend screening have a 25% (RR 0.75, CI: 0.66 - 0.84) reduction in their risk of death (29).Wipe-based POCT gFOB kits are available to improve ease of sampling but evidence suggests that they result in a greater number of positive, weak positive (requiring repeat testing), and un-testable (e.g. inadequate stool, torn collection paper) results compared with usual gFOB, resulting in too great a demand for colonoscopy or repeat tests (38). One wipe gFOB

technique resulted in a very low yield of significant disease and authors, as in the studies of symptomatic patents, discounted this method as a viable screening option (38).

gFOB vs. FIT

A Cochrane Diagnostic Test Accuracy (DTA) review protocol was published in 2011 to investigate whether gFOB can be replaced by FIT for primary CRC screening (39). An RCT from the Dutch screening programme demonstrated that detection rates for advanced neoplasia are significantly higher for laboratory-based quantitative FIT (OR 2.4% 95% CI 1.3-4.1) than for gFOB for screening an asymptomatic average-risk population (23). There is also evidence from numerous diagnostic accuracy studies that laboratory-based quantitative FIT has higher sensitivity and specificity for CRC than gFOB, especially for detecting high-risk adenomas (28, 31, 40-43). A review of cohort studies for the BCSP found wide ranges of sensitivity and specificity for FIT for all neoplasms (5.4-19.8% and 91.6- 98.5%, respectively), whereas case-control studies reported higher sensitivities and specificities as expected by the study design (38.9-68.9% and 93.9-98.3%). For CRC specifically, sensitivity was 23.7-91.0% and specificity 77.1-98.9%, and for all adenomas sensitivity was 4.4-91.0% and specificity 42.8-98.5% (44). However the inclusion criteria grouped quantitative and qualitative FITs, and so did not account for the variation in accuracy created by grouping qualitative FIT kits with different thresholds. Health technology appraisals have so far focussed on quantitative techniques due to the potential for automation and reduced inter-observer variation, and qualitative FOBT have not been included as the test is done by the patient outside of a controlled clinical setting (45).

For detection of CRC, advanced neoplasm, and any neoplasm a comparative analysis enrolling 2235 patients showed laboratory-based quantitative FIT were more sensitive than laboratory-based gFOB (Table. 2). Overall FIT detected twice as many neoplasms and three times as many advanced neoplasms and higher PPVs were associated with fewer colonoscopies needed to detect one neoplasm. Whilst accuracy was consistently higher for FIT there was variation between FIT kits (40). A larger study of 85,149 average-risk individuals from the French CRC screening programme also showed superior accuracy of automated quantitative FIT to gFOB but with little variation between quantitative FIT techniques (46).

Table 2: comparative accuracy of laboratory-based gFOB and laboratory-based quantitative FIT (40).

	Sensitivity (%)			Specificity (%)		
	Colorectal Cancer	Advanced Neoplasm	Any Neoplasm	Colorectal Cancer	Advanced Neoplasm	Any Neoplasm
Laboratory-based gFOB						
HemOccult	33.3	8.6	5.5	95.2	95.4	95.2
Lab-based quantitative FIT						
RIDASCREEN Haemoglobin	60.0	23.4	11.5	95.4	97.1	97.5
RIDASCREEN Haemoglobin-haptoglobin Complex	53.3	20.3	10.2	95.4	96.8	97.1
OC SENSOR	73.3	25.7	12.1	95.5	97.4	97.8

Quantitative laboratory-based FIT vs qualitative FIT.

To address potential variability between FITs (30, 47) a large German inter-test agreement study of one laboratory-based quantitative FIT (RIDASCREEN) and 6 point-of-care qualitative FITs (ImmunoCARE-C, FOB advanced, PreventID CC, Bionexia FOBplus, QuickVue iFOB, Bionexia Hb/Hp Complex) demonstrated that there is good inter-test agreement between kits that use similar thresholds, suggesting there is no major variation in diagnostic accuracy outside of that produced by grouping together kits using different thresholds for a positive result (40). These results were verified by a later study (48). This has led to recommendations that manufacturers should adapt the thresholds used, and tailor their instructions on how to handle borderline results to suit the population being screened, and that major efforts should be made to develop common standards for the reporting FIT performance (40, 48).

Single vs multiple-sample qualitative FIT.

There is some evidence suggesting that single-sample FIT testing could perform as accurately as two-sample testing if the appropriate threshold was chosen in relation to the population being screened, but there is conflicting evidence that up to two thirds of advanced neoplasms can be missed by single or double FIT sampling, indicating that there is still a potential issue of quality assurance between qualitative FIT kits (49, 50). The literature describes a necessary trade-off between single sampling that relies on large heavily bleeding lesions and the fluctuant bleeding seen with smaller lesion more suited to repeat sampling (49). One suggestion is to increase sensitivity at the cost of specificity by lowering the cut-off value of single FIT sampling instead of improving specificity by using two (or more) sample testing, but there are concerns that this will overburden colonoscopy services (49-51). There is no conclusive evidence that one-sample FIT would improve screening uptake at a population level, despite many speculating it would (49).

Impact compared to existing technology

FOBt has consistently been shown to have better uptake than flexible sigmoidoscopy, and meta-analysis of seven studies has shown that screening participation rates are significantly higher for FIT compared to gFOB (RR 1.21; 95% CI 1.09-1.33) and later RCT and Cohort study evidence supports this (52-60), possibly due to the lack of need for dietary changes prior to testing. The simplified procedural requirements of qualitative FIT resulting in greater convenience are further associated with gains in acceptability and participation (15, 58). Another role of FIT may be as a second line test, to manage borderline gFOB results with a second-line FIT to reduce false positives from first-line gFOB (61-63).

Guidelines and Recommendations

"Duffy MJ., et al. Tumor Markers in Colorectal Cancer, Gastric Cancer and Gastrointestinal Stromal Cancers: European Group on Tumor Markers (EGTM) 2013 Guidelines Update. Int. J. Cancer 'Accepted Article', doi: 10.1002/ijc.28384"– Recommended biomarkers for colorectal cancer include a FIT in screening asymptomatic subjects ≥n screening asymptomCRC.

"NICE. Referral guidelines for suspected cancer. NICE April 2011"- does not recommend the use of FOBt stating that for patients with abdominal symptoms, the sensitivity, specificity, and positive predictive values of FOBt are too low to make these tests helpful (3).

"Labianca R., et al. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. Annals of Oncology 2010 21(Supplement 5):v70–v77"- states if screening programmes for colorectal cancer are implemented they should use the FOBt, whereas colonoscopy should be used for the follow-up of test-positive cases, but does not specify what type of FOBt. (64)

Research Questions:

For screening for CRC, there are several unanswered questions:

- Is home-administered one-step qualitative FIT accurate enough for use in CRC screening?
- What is the comparative accuracy of home one-step vs. clinician based one-step qualitative FIT?
- Can GP recommended one-step FIT improve uptake of CRC screening in hard to reach groups?
- What is the impact on GP workload of introducing POCT FIT into the screening setting?
- Is one-step FIT a cost effective alternative for CRC screening?

For diagnostic evaluation of symptomatic patients to rule out CRC:

- Can GP-based one-step FIT be used as a discriminatory triage test to inform 2 week wait referral decisions?
- Is home-based one-step FIT as accurate and reliable as GP based one-step FIT in symptomatic patients?
- What is the psychological impact of receiving immediate FIT test results at home?

Suggested next steps:

For screening for CRC:

- Diagnostic test accuracy study to compare home one-step FIT (performed at home by patient) with laboratory based FIT testing; to establish the optimum qualitative FIT thresholds for use at home in different screening populations.

- Economic evaluation to establish the feasibility of home one-step FIT screening.

For diagnostic evaluation of symptomatic patients to rule out CRC:

- Diagnostic accuracy study comparing the available one-step qualitative FITs when used in a clinical environment by a general practitioner compared with laboratory FIT.
- Large diagnostic accuracy studies investigating the utility of one-step qualitative FIT as a triage test to rationalise referrals to secondary care.

Expected outcomes:

Given that evidence exists that comparable diagnostic accuracy can be achieved between FITs (if attention is given to the thresholds used) and that FIT is more accurate than gFOB, the clear procedural advantages of the one-step, single stool, home sampling are undeniable. As involving GPs appears to improve uptake, GP recommended home FIT could improve screening uptake, and home FIT could be used to inform diagnostic reasoning in symptomatic patients prior to referral. The lack of explicit evidence on the comparative accuracy of one-step home qualitative FIT kits needs urgent attention in the asymptomatic screening and symptomatic settings.

References:

1. Jellema P, van der Windt DA, Bruinvels DJ, Mallen CD, van Weyenberg SJ, Mulder CJ, et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. BMJ. 2010;340:c1269. PubMed PMID: 20360221. Pubmed Central PMCID: 2848719.
2. Maringe C WS, Rachet B, Butler J, Fields T, Finan P, Maxwell R, Nedrebo B, Pahlman L, Sjovall A, Spigelman A, Engholm G, Gavin A, Gjerstorff L, Hatcher J, Johannesen TB, Morris E, McGahan CE, Tracey E, Turner D, Richards MA, Coleman MP. Stage at diagnosis and colorectal cancer survival in six high-income countries: A population-based study of patients diagnosed during 2000–2007. Acta Oncologica. 2013;52(5):919-32. PubMed PMID: 23581611.
3. NICE. Referral for suspected cancer (CG27). National Institute of Clinical Excellence. Accessed via http://www.nice.org.uk/nicemedia/pdf/cg027publicinfo.pdf, 2005.
4. Which? 5 need to knows about home self-test health kits 2011. Available from: http://www.which.co.uk/news/2011/03/5-need-to-knows-about-home-self-test-health-kits-249152/.
5. NHS Choices. Warning about self-test health kits 2011. Available from: http://www.nhs.uk/news/2011/03March/Pages/warning-on-self-test-health-kits.aspx, .
6. Mail Online. Do DIY testing kits really work? Available from: http://www.dailymail.co.uk/health/article-163402/Do-DIY-testing-kits-really-work.html.
7. Adelstein BA, Macaskill P, Chan SF, Katelaris PH, Irwig L. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. BMC Gastroenterol. 2011;11:65. PubMed PMID: 21624112. Pubmed Central PMCID: 3120795.
8. Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners. 2011 May;61(586):e231-43. PubMed PMID: 21619747. Pubmed Central PMCID: 3080228.
9. Hamilton W, Round A, Sharp D, Peters TJ. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. Br J Cancer. 2005 Aug 22;93(4):399-405. PubMed PMID: 16106247. Pubmed Central PMCID: 2361578.

10. Hippisley-Cox J, Coupland C. Identifying patients with suspected colorectal cancer in primary care: derivation and validation of an algorithm. The British journal of general practice : the journal of the Royal College of General Practitioners. 2012 Jan;62(594):e29-37. PubMed PMID: 22520670. Pubmed Central PMCID: 3252537.

11. Goodyear SJ, Stallard N, Gaunt A, Parker R, Williams N, Wong L. Local impact of the English arm of the UK Bowel Cancer Screening Pilot study. The British journal of surgery. 2008 Sep;95(9):1172-9. PubMed PMID: 18690636.

12. Dukes CE. The classification of cancer of the rectum. The Journal of Pathology and Bacteriology. 1932;35(3):323-32.

13. Hoff G, Dominitz JA. Contrasting US and European approaches to colorectal cancer screening: which is best? Gut. 2010 Mar;59(3):407-14. PubMed PMID: 20207645.

14. von Euler-Chelpin M, Brasso K, Lynge E. Determinants of participation in colorectal cancer screening with faecal occult blood testing. Journal of public health. 2010 Sep;32(3):395-405. PubMed PMID: 20015868.

15. Lo SH, Waller J, Wardle J, von Wagner C. Comparing barriers to colorectal cancer screening with barriers to breast and cervical screening: a population-based survey of screening-age women in Great Britain. J Med Screen. 2013 Jun 10. PubMed PMID: 23761420.

16. Ellis RJ, Wilson S, Holder RL, McManus RJ. Different faecal sampling methods alter the acceptability of faecal occult blood testing: a cross sectional community survey. Eur J Cancer. 2007 Jun;43(9):1437-44. PubMed PMID: 17475476.

17. Koo JH, Arasaratnam MM, Liu K, Redmond DM, Connor SJ, Sung JJ, et al. Knowledge, perception and practices of colorectal cancer screening in an ethnically diverse population. Cancer Epidemiol. 2010 Oct;34(5):604-10. PubMed PMID: 20580631.

18. Le Breton J, Journy N, Attali C, Le Corvoisier P, Brixi Z, Bastuji-Garin S, et al. Improving participation in colorectal cancer screening: targets for action. Prev Med. 2012 Nov;55(5):488-92. PubMed PMID: 22926013.

19. Ealey J, Meade CD, Gwede CK, Quinn G, Abdulla R, Vadaparampil S, et al. Patients' perspectives on immunochemical fecal occult blood test (I-FOBT or FIT): Not your father's FOBT. Cancer Epidemiology Biomarkers and Prevention. 2011 September;20 (10 Meeting Abstracts). PubMed PMID: 70707101.

20. Cole SR, Smith A, Wilson C, Turnbull D, Esterman A, Young GP. An advance notification letter increases participation in colorectal cancer screening. Journal of Medical Screening. 2007;14(2):73-5. PubMed PMID: 17626705.

21. Libby G, Bray J, Champion J, Brownlee LA, Birrell J, Gorman DR, et al. Pre-notification increases uptake of colorectal cancer screening in all demographic groups: a randomized controlled trial. J Med Screen. 2011;18(1):24-9. PubMed PMID: 21536813. Epub 2011/05/04. eng.

22. Sequist TD, Zaslavsky AM, Marshall R, Fletcher RH, Ayanian JZ. Patient and physician reminders to promote colorectal cancer screening: a randomized controlled trial. Archives of Internal Medicine. 2009 Feb 23;169(4):364-71. PubMed PMID: 19237720. Pubmed Central PMCID: Source: NLM. NIHMS73290 Source: NLM. PMC2683730.

23. Hol L, van Leerdam ME, van Ballegooijen M, van Vuuren AJ, van Dekken H, Reijerink JCIY, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut. 2010 Jan;59(1):62-8. PubMed PMID: 19671542.

24. Zajac IT, Whibley AH, Cole SR, Byrne D, Guy J, Morcom J, et al. Endorsement by the primary care practitioner consistently improves participation in screening for colorectal cancer: a longitudinal analysis.[Erratum appears in J Med Screen. 2010 Jun;17(2):106]. Journal of Medical Screening. 2010;17(1):19-24. PubMed PMID: 20356941.

25. Hewitson P, Ward AM, Heneghan C, Halloran SP, Mant D. Primary care endorsement letter and a patient leaflet to improve participation in colorectal cancer screening: results of a factorial randomised trial. Br J Cancer. 2011 Aug 9;105(4):475-80. PubMed PMID: 21829202. Pubmed Central PMCID: 3170960.

26. Potter MB, Walsh JM, Yu TM, Gildengorin G, Green LW, McPhee SJ. The effectiveness of the FLU-FOBT program in primary care a randomized trial. Am J Prev Med. 2011 Jul;41(1):9-16. PubMed PMID: 21665058.

27. Senore C, Ederle A, Benazzato L, Arrigoni A, Silvani M, Fantin A, et al. Offering people a choice for colorectal cancer screening. Gut. 2013 May;62(5):735-40. PubMed PMID: 22442162.

28. Duffy MJ. Screening for colorectal cancer: Which is the best biochmical test? Tumor Biology. 2010 August;31:S23. PubMed PMID: 70437906.

29. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews. 2007 (1):CD001216. PubMed PMID: 17253456. Epub 2007/01/27. eng.

30. Haug U, Hundt S, Brenner H. Quantitative immunochemical fecal occult blood testing for colorectal adenoma detection: evaluation in the target population of screening and comparison with qualitative tests. The American journal of gastroenterology. 2009;105(3):682-90.

31. Brenner H, Haug U, Hundt S. Inter-test agreement and quantitative cross-validation of immunochromatographical fecal occult blood tests. International Journal of Cancer. 2010;127(7):1643-9.

32. Lucas AL, Hwang C, Frucht H. Strengthening the Case for Stool DNA Tests as First-Line Colorectal Cancer Screening: Are We There Yet? Clinical Gastroenterology and Hepatology. 2012 3//;10(3):214-5.

33. Ahlquist DA, Zou H, Domanico M, Mahoney DW, Yab TC, Taylor WR, et al. Next-Generation Stool DNA Test Accurately Detects Colorectal Cancer and Large Adenomas. Gastroenterology. 2012 2//;142(2):248-56.

34. Pye G, Jackson J, Thomas WM, Hardcastle JD. Comparison of Coloscreen Self-Test and Haemoccult faecal occult blood tests in the detection of colorectal cancer in symptomatic patients. The British journal of surgery. 1990 Jun;77(6):630-1. PubMed PMID: 2200550. Epub 1990/06/01. eng.

35. Tate JJT, Northway J, Royle GT, Taylor I. Faecal occult blood testing in symptomatic patients: Comparison of three tests. British Journal of Surgery. 1990;77(5):523-6.

36. Verne J, Kettner J, Mant D, Farmer A, Mortenson N, Northover J. Self-administered faecal occult blood tests do not increase compliance with screening for colorectal cancer: results of a randomized controlled trial. Eur J Cancer Prev. 1993 Jul;2(4):301-5. PubMed PMID: 8358281. Epub 1993/07/01. eng.

37. Kaul A, Shah A, Magill FH, Hawkins SA, Skaife P. Immunological faecal occult blood testing: a discriminatory test to identify colorectal cancer in symptomatic patients. International Journal Of Surgery. 2013;11(4):329-31. PubMed PMID: 23459187.

38. Fraser C, McDonald P, Colford L, Irvine A, Kenicer M, Morton C, et al. Experience with a wipe guaiac-based faecal occult blood test as an alternative test in a bowel screening programme. Journal of Medical Screening. 2010;17(4):211-3.

39. Van Roon AHC, Goede SL, Van Ballegooijen M, Van Vuuren AJ, Looman CWN, Biermann K, et al. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening

Comparative evaluation of nine faecal immunochemical tests for the detection of colorectal cancer. Gut. 2013 March;62(3):409-15. PubMed PMID: 2013087232.

40. 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 Sep;49(14):3049-54. PubMed PMID: 23706981.

41. 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. European Journal of Cancer. 2008 Oct;44(15):2254-8. PubMed PMID: 18760592.

42. Park DI, Ryu S, Kim Y-H, Lee S-H, Lee CK, Eun CS, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. American Journal of Gastroenterology. 2010 Sep;105(9):2017-25. PubMed PMID: 20502450.

43. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, Nicolas D, Moreno SG, Jimenez A, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. Journal of gastroenterology. 2010 Jul;45(7):703-12. PubMed PMID: 20157748.

44. Whyte S, Chilcott J, Cooper K, Essat M, Stevens J, Wong R, et al. Re-appraisal of the options for colorectal cancer screening FULL REPORT. Sheffield Univeristy: School of Health and Related Research (ScHARR), 2011.

45. K SW, J B, Duffy MJ. Diagnostic accuracy and cost-effectiveness of faecal occult blood tests (FOBT) used in screening for colorectal cancer: a systematic review CRD: University of York, 2007.

46. Faivre J, Dancourt V, Denis B, Dorval E, Piette C, Perrin P, et al. Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer. European Journal of Cancer. 2012 Nov;48(16):2969-76. PubMed PMID: 22572481.

47. Hoepffner N, Shastri YM, Hanisch E, Rosch W, Mossner J, Caspary WF, et al. Comparative evaluation of a new bedside faecal occult blood test in a multicentre study. Aliment Pharmacol Ther. 2006 Jan 1;23(1):145-54. PubMed PMID: 16393292. Epub 2006/01/06. eng.

48. Tao S, Brenner H. Well adjusted qualitative immunochemical faecal occult blood tests promising alternative for inexpensive, high-quality colorectal cancer. Eur J Cancer Prev. 2013 Jul;22(4):305-10. PubMed PMID: 23702679. Epub 2013/05/25. eng.

49. Guittet L, Bouvier V, Guillaume E, Levillain R, Ruiz A, Lantieri O, et al. Colorectal cancer screening: why immunochemical faecal occult blood test performs as well with either one or two samples. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2012 Aug;44(8):694-9. PubMed PMID: 22525156.

50. Terhaar sive Droste JS, van Turenhout ST, Oort FA, van der Hulst RWM, Steeman VA, Coblijn U, et al. Faecal immunochemical test accuracy in patients referred for surveillance colonoscopy: a multi-centre cohort study. BMC Gastroenterology. 2012;12:94. PubMed PMID: 22828158. Pubmed Central PMCID: Source: NLM. PMC3444435.

51. Oort FA, van Turenhout ST, Coupe VMH, van der Hulst RWM, Wesdorp EIC, Terhaar sive Droste JS, et al. Double sampling of a faecal immunochemical test is not superior to single sampling for detection of colorectal neoplasia: a colonoscopy controlled prospective cohort study. BMC Cancer. 2011;11:434. PubMed PMID: 21985604. Pubmed Central PMCID: Source: NLM. PMC3201938.

52. Cole S, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. Journal of Medical Screening. 2003;10(3):117-22.

53. Federici A, Giorgi Rossi P, Borgia P, Bartolozzi F, Farchi S, Gausticchi G. The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomized controlled trial. Journal of Medical Screening. 2005;12(2):83-8. PubMed PMID: 15949119.

54. Hol L, de Jonge V, van Leerdam ME, van Ballegooijen M, Looman CWN, van Vuuren AJ, et al. Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. European Journal of Cancer. 2010 Jul;46(11):2059-66. PubMed PMID: 20621736.

55. Hol L, Wilschut JA, van Ballegooijen M, van Vuuren AJ, van der Valk H, Reijerink JCIY, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. British Journal of Cancer. 2009 Apr 7;100(7):1103-10. PubMed PMID: 19337257. Pubmed Central PMCID: Source: NLM. PMC2670000.

56. Hughes K, Leggett B, Mar CD, Croese J, Fairley S, Masson J, et al. Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community. Australian and New Zealand journal of public health. 2005;29(4):358-64.

57. Levi Z, Birkenfeld S, Vilkin A, Bar-Chana M, Lifshitz I, Chared M, et al. A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate. A prospective, controlled, feasibility study. Int J Cancer. 2011 May 15;128(10):2415-24. PubMed PMID: 20658527. Epub 2010/07/27. eng.

58. Liles EG, Perrin N, Rosales AG, Feldstein AC, Smith DH, Mosen DM, et al. Change to FIT increased CRC screening rates: evaluation of a US screening outreach program. American Journal of Managed Care. 2012 Oct;18(10):588-95. PubMed PMID: 23145804. Pubmed Central PMCID: Source: NLM. NIHMS444651 Source: NLM. PMC3631273.

59. Van Rossum LG, Van Rijn AF, Verbeek AL, Van Oijen MG, Laheij RJ, Fockens P, et al. A cost-effectiveness analysis in colorectal cancer screening comparing immunochemical faecal occult blood tests with guaiac faecal occult blood tests and no screening. Gastroenterology. 2009 May;1):A331. PubMed PMID: 70152097.

60. Vart G, Banzi R, Minozzi S. Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis. Preventive Medicine. 2012 Aug;55(2):87-92. PubMed PMID: 22634386.

61. Fraser CG, Digby J, McDonald PJ, Strachan JA, Carey FA, Steele RJC. Experience with a two-tier reflex gFOBT/FIT strategy in a national bowel screening programme. Journal of Medical Screening. 2012 Mar;19(1):8-13. PubMed PMID: 22156144.

62. Fraser CG, Mathew CM, Mowat NAG, Wilson JA, Carey FA, Steele RJC. Evaluation of a card collection-based faecal immunochemical test in screening for colorectal cancer using a two-tier reflex approach. Gut. 2007 Oct;56(10):1415-8. PubMed PMID: 17309886. Pubmed Central PMCID: Source: NLM. PMC2000260.

63. Fraser CG, Matthew CM, Mowat NAG, Wilson JA, Carey FA, Steele RJC. Immunochemical testing of individuals positive for guaiac faecal occult blood test in a screening programme for colorectal cancer: an observational study. Lancet Oncology. 2006 Feb;7(2):127-31. PubMed PMID: 16455476.
64. Labianca R, Nordlinger B, Beretta GD, Brouquet A, Cervantes A, Group EGW. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2010 May;21 Suppl 5:v70-7. PubMed PMID: 20555107.

Authors: Brian Nicholson, Matthew Thompson, Christopher P. Price, Carl Heneghan, Annette Plüddemann

Contact details: Dr. Annette Plüddemann; Email: dec@phc.ox.ac.uk