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A review of the UK National Bowel Cancer Screening Programme and alternative options

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The UK National Bowel Cancer Screening Programme

- Colorectal cancer (CRC) is the 4th most common cancer in the UK, and the 3rd most common cause of cancer death.[1]
- When detected early, or in its premalignant stages, mortality is significantly reduced; 1-year survival may reach 98% in stage I disease, but only 40% in stage IV.[1]
- Its distinct latent phase, high incidence, treatable pre-cursor and well-characterised molecular pathogenesis all satisfy Wilson and Junger criteria for screening.[2]

What does the current Bowel Cancer Screening Programme involve?

Faecal Occult Blood testing (FOBt)[3]

- Men and women
- From 60-74 years, biennially
- Guaiac-based test of a panel of stool samples for blood
- Can be done at home and sent to the lab in the post
- Colonoscopy if blood is present

One-off Flexible Sigmoidoscopy[4]

- Men and women
- Once, at 55 years
- Distal bowel endoscopy
- One of >60 local screening centres in England
- Visualised abnormalities are investigated by full colonoscopy

The history of UK bowel cancer screening

- Adequate screening strategies should reduce disease mortality, and where a pre-malignant phase is easily definable, reduce incidence.[2]
- Globally, multiple trials show that UK CRC screening tools meet such requirements.[5-7]

1981-1995: The Nottingham RCT of FOBt screening yielded a 15% reduction in cumulative CRC mortality[5]

1998: The first UK trial of one-off flexible sigmoidoscopy screening detected adenomas in 10% and cancers in 7 per 1000 screenees.[8]

1999-2005: The UK CRC Screening Pilot study had an estimated sensitivity of 57.7-64.4%.[9] It was supported by most primary care staff despite increased workload.[10]

2006: The National FOBt Screening Programme was introduced.[10]

Haemoccult testing – changes to the current standard

- Subclinical malignancies and pre-malignant lesions are susceptible to small, unnoticed hemorrhages.
- 'Haemoccult' screening detects these to identify high-risk individuals warranting further investigation.
- FOBt is the current mainstay haemoccult test in the UK; see Figure 1.[11]
- From December 2018, FOBt will gradually be replaced by Faecal Immunochemical Testing (FIT); a novel antibody-based haemoccult test.[4,12,13]
- This change brings with it opportunity to reduce the screening age to 50 years; this is in line with Scotland and has a good evidence base for detecting CRC at an earlier stage.[14]

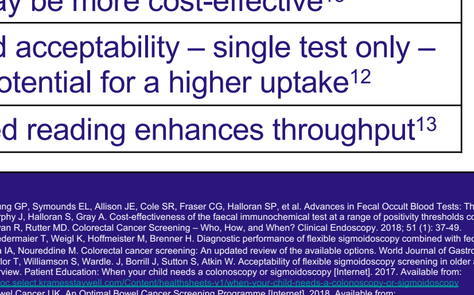


Figure 1 – FOBt; self-taken stool samples are placed onto Guaiac paper. Taken from[11].

Why implement a phased change to FIT testing?	
Guaiac-based (FOBt)	**Immunochemical (FIT)**
Moderate sensitivity; ~30.8-74.2%[12]	Improved sensitivity; ~87.1-92.3% if a low positivity threshold (20µg/g) is applied[12]
Cross-reactivity with dietary peroxidases makes this test inherently non-specific[12]	Human haemoglobin-specific antibodies; dietary interference is unlikely[12]
Binary; either positive or negative	Quantitative; allows for adjustable positivity threshold and increased flexibility for recall – may be more cost-effective[13]
Multiple samples needed – 6 samples from 3 separate stools – less acceptable[12]	Increased acceptability – single test only – so potential for a higher uptake[12]
Manual oxidisation and analysis[13]	Automated reading enhances throughput[13]

Bowel Scope Screening; flexible sigmoidoscopy (FS)

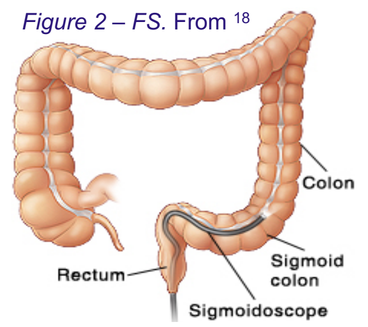


Figure 2 – FS. From [18]

- FS has an established evidence-base, reducing both incidence and mortality.[8,15,16]
- It requires little bowel preparation relative to colonoscopy.[16]
- Despite a reported high acceptability amongst those screened, uptake is only ~44-47%.[16,17]
- Moreover, FS visualizes the distal colon and rectum only; its benefits in proximal lesions are limited unless referral is warranted; see Figures 2 and 3.[16,18]
- Roll-out issues due to limited resources mean that only ~43% of UK GPs currently provide FS; <50% of the target population are invited.[19]

A role for colonoscopy or imaging?

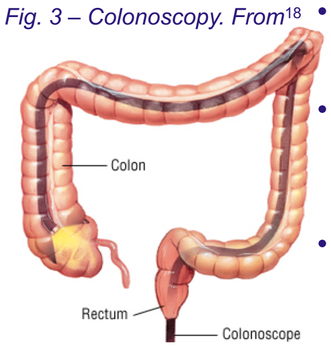


Fig. 3 – Colonoscopy. From[18]

- 10-yearly colonoscopy is a key screening option in the USA, and is opted for by 90% of those screened, despite its highly invasive nature.[2]
- So far no randomised controlled trial data supports colonoscopy as the gold-standard, but observational data is promising; one meta-analysis concluded a 68% lower overall CRC mortality in those screened.[16]
- CT colonography may be more acceptable but involves radiation exposure, extensive bowel preparation and is a less sensitive test.[20]

Novel approaches to bowel cancer screening

Faecal DNA biomarkers:

- This relies on the luminal exfoliation of cells from cancerous and pre-cancerous lesions.[21]
- The only FDA-approved version – Cologuard® - is multi-targeting; it detects faecal mutant kras and β-actin, alongside epigenetic features of microsatellite instability.[16,21]
- Despite enhanced sensitivity, Cologuard® FIT-DNA is less specific than FIT alone, and has limited detection of pre-cancerous lesions, reducing preventative capacity.[16,20-22]

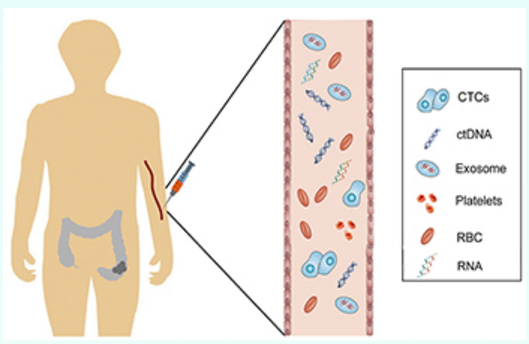


Figure 4 – Liquid biopsy only requires basic venipuncture, and hence confers increased acceptability. Adapted from [24].

The "Liquid biopsy":

- Allows for somatic mutation screening of circulating cell-free tumour DNA (CtDNA) and other plasma constituents; see Figure 4.[23,24]
- Recently FDA-approved Epi-Procolon® detects mutated methylated septin9 DNA in CtDNA shed from the gut into plasma in CRC.[16,23]
- Epi-Procolon has high sensitivity for CRC itself but almost no preventative capacity.[16]

Discussion & future directions

- The UK has utilized the non-invasive properties of FOBt and the sensitivity of FS, yet the annual uptake of FOBt remains at only 59%, and FS uptake is even lower.[17,19]
- In 2015, the National Screening Committee recommended FIT above FOBt, however the increased sensitivity of a 20µg/g threshold will increase demand on colonoscopy services.
- The NHS is unlikely to have sufficient endoscopy services, pathology resources or clinicians to meet demands at high sensitivity testing, unless FS is decommissioned.
- A recent NSC review found that combining the proposed FIT screening with one-off flexible sigmoidoscopy as it is currently running is not cost-effective.[19]

Proposed changes to the UK Bowel Cancer Screening Programme[19]

- **Phased transition to biennial FIT at 50-74yrs**
- **Gradual decommissioning of one-off Bowel Scope Screening at 55 years**

Conclusions

- There are many CRC screening options, however some are highly invasive and will always yield a reduced uptake.
- The evidence-base behind biomarkers in screening is growing, and non-invasive tools such as the liquid biopsy may help to yield a higher screening uptake in the future.
- The UK CRC Screening Programme must be evidence-based, but aside from this, the NHS can only undertake what is economically feasible and deemed cost-effective.
- More extensive colonoscopy services would enhance the flexibility of CRC screening.

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