Population-based Screening in Colorectal Cancer - Current Practice and Future Developments: Faecal Biomarkers Review

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INTRODUCTION

Colorectal cancer (CRC) is a major cause of mortality and morbidity in Europe and worldwide, with an estimated European incidence of 43.5 per 100,000 head of population in 2012 and mortality of 19.5 per 100,000 [1]. UK lifetime risk lies at 1 in 15 for men or 1 in 19 for women [2], with a similar incidence in Europe [1]; this incidence is increasing. Colorectal cancer predominantly affects men and women over the age of 75 and is one of the major causes of cancer death, with a 50.7% 5 year mortality rate [3]. There is evidence for a strong genetic component in many cancers, yet more than 90% of CRCs are sporadic, developing from adenomatous polyps over a 10- to 15-year period, through an adenoma-carcinoma sequence, which is likely to be similar to that hypothesised by Vogelstein [4]. The hypothesis identifies a multi-step process of neoplastic change, from an abnormal crypt focus to adenomatous change to frank malignancy. The pathological model has become increasingly refined since first suggested over 25 years ago, with clearly associated clusters of mutations at each step, such as APC and k-ras [5]. One might argue that the major consideration in improving the management of CRC is the potential for early diagnosis. A comparison of 5-year survival rates from Duke's staging of CRC (A, the most superficial, 93.2%, compared with C 47.7% and D, distant metastatic spread, 6.6%) [3] clearly demonstrates the potential value of a proactive approach. The existence of pre-cancerous lesions, which can be readily identified and removed during a single colonoscopy procedure in the majority of cases [6] gives a powerful argument for a screening programme directed at the most susceptible members of the population.

CURRENT PRACTICE

The 2013 European guidelines for CRC screening suggest faecal occult blood testing (FOBt) between ages 50-74, as an
initial test, and recommend that colonoscopy should remain
the gold standard [7, 8]. They provide a synthesis of evidence
to support member states in maintaining or establishing such
a programme [9]. This reflects the heterogeneous combination
of national/regional programmes and non-population based
screening found in many European nations, as identified in
a recently published assessment by Altobelli et al [8]. Many
national screening guidelines are available, including FOBt,
colonoscopy, flexible sigmoidoscopy (FS), CT colonography
(CTC), faecal DNA testing and double contrast barium enemas
[7, 10-16].

Screening for CRC in the UK is currently performed using
biennial non-rehydrated guaiac-based faecal occult blood
tests (FOBt: Hema-screen; Immunostics Inc., Ocean, New
Jersey, USA) and colonoscopy; a scheme proven to reduce
CRC-related mortality [17, 18]. A Cochrane systematic
review demonstrated a 16% relative risk reduction from four
large studies using the above technique [18], while the cost-
efficiency of such an approach has been well-established over
endoscopy alone [19, 20]. Two forms of FOBt (immunological
e.g. OC-Sensor and guaiac e.g. Hemoccult-II) are currently
available and used for screening purposes worldwide. However
there are several potential pitfalls with this approach: those
associated with the uptake and acceptability of such tests by
the public, concerns over the sensitivity and specificity of FOBt
and endoscopy, the small but significant risk of complications
associated with the endoscopic procedure itself and, finally,
the economic burden of an extensive lower gastrointestinal
endoscopy service.

UPTAKE AND ACCEPTABILITY OF
FAECAL OCCULT BLOOD TESTING
BY THE PUBLIC

The success of any screening programme depends upon
the acceptability and uptake of the tests by the public. A
review of the first 6 years of the UK Bowel Cancer Screening
Programme (BCSP) described an uptake rate of 55.35% in
the over 16 million invitees, from June 2006 to the end of
2012: 88% in the incident round and 45% in prevalent rounds
[2]. Of the returned kits, 2.08% proved to be FOBt positive,
90.49% of those with positive kits underwent intervention,
of which 84% involved colonoscopy [2]. This suggests that
the “rate limiting step” for screening uptake lies in the faecal test
itself or public awareness of the importance of CRC screening,
especially as uptake for cervical and breast cancer screening in
the UK has been measured at 82% and 73% respectively over a
similar period [21, 22]. A series of studies have identified
that acceptability is partly determined by the practicalities of
collection, transport and storage of the stool, together with
perceptions of the endoscopy test associated with a positive
sample and, most notably, an understanding of the nature and
purpose of the screening programme [23-25].

Guaiac-based FOBts, such as that used in the UK, requires
two collections of small amounts of faecal matter from three
successive separate motions. No dietary restrictions are
required [2]. An unclear test (one to four positive samples out
of the six provided) requires a further test to be performed and,
if any samples are positive, referral is made for endoscopy. If
none are positive, a final test is sent under the same inclusion
criteria [2]. Immunological tests, such as that used in Italy [26],
usually require one collection from three consecutive motions.
There is also no requirement to alter diet or medication with
the immunological FOBt, potentially increasing concordance.
This is supported by a meta-analysis performed by Vart et
al, suggesting that the process involved in collection of the
immunological test was perceived as more simple overall [27],
although it is likely that this may vary to some degree with the
kit in question.

THE SENSITIVITY AND SPECIFICITY OF
FAECAL OCCULT BLOOD TESTING AND
ENDOSCOPY

Several recent articles have summarised the evidence
behind screening using FOBts and compared immunological
and guaiac approaches [2, 9, 14-18, 28-31]. Traditionally, the
guaiac test has delivered the highest combination of sensitivity,
specificity and cost-efficiency [18]. It has therefore formed the
basis of the majority of community screening programmes [32],
though with considerable variation in outcome [29]. Recent
studies have highlighted improvements to the immunological
test which have pushed it ahead of the guaiac test in terms
of overall efficacy [28-31]. A 2010 meta-analysis identified
a comparative sensitivity and specificity of 67% and 85% for
immunological FOBt compared to 54% and 80% for guaiac
FOBt [28]. Increased participation rates and higher overall
detection rates have also been noted [27, 28]. A cost-benefit
analysis of immunological FOBt, performed by Wilschut et al,
determined that biennial screening with a cut-off of 50ng/ml
would prove most efficacious, at €14,000 per life year gained,
for an asymptomatic population aged 55-75 [33]. The ability to
quantify a FOB result potentially allows the establishment of a
national cut-off level, localised adjustment of this figure in line
with local healthcare funding priorities and greater potential
for integration with alternative screening tools. Such a degree
of subtlety is lacking in guaiac testing kits and, as a result, the
UK Bowel Cancer Screening Programme (BCSP) has plans to
introduce immunological testing kits forthwith [32].

Nonetheless, there are major flaws inherent in the essential
modality of detecting FOB. Recent evidence suggests that
sensitivity and positive predictive value of both quantitative
and qualitative FOBts were much higher in men than women, while
specificity and negative predictive value were substantially
lower for men. Such data are only partly explained by sex-
related differences in adenoma-carcinoma presentation [34].
The risk of false results from such confounding factors as red
meat intake, vegetables and vitamin C, might be mitigated to
some extent by the use of immunological FOBt but some risk
of false positive results remains from upper gastrointestinal
sources of bleeding and around storage of the testing kits [8].
Moreover, a potential tumour must induce bleeding to be
detected by an FOB test. This is a factor far more common
in the mostly left-sided polyloid lesions which comprise
approximately 85% of CRC [35]; by implication omitting the
other 15% of CRC which have a tendency towards a sessile
phenotype and which are less likely to present with bleeding
[36]. Right-sided cancers were more likely to have an abnormal
FOBt and be at a more advanced stage than left sided, when presenting to the UK BCSP [37]. Colonoscopy and flexible sigmoidoscopy (FS) have been widely examined as part of screening programmes and are frequently required for further investigation and treatment of any lesions identified through other means [2, 30, 38, 39]. Colonoscopy is currently the gold standard for both screening and treatment, though with little support from RCT data and variable outcomes in many studies, frequently dependent on the quality of the colonoscopy procedure [6, 40-42]. A recent meta-analysis of colonoscopy in an asymptomatic screening population identified an average sensitivity of 88.8%, with associated specificity of 75.4% [42]. Several back-to-back studies have shown an estimated colonoscopic miss-rate of between 20 and 25%, as well as identifying that 3-8% of patients with CRC had undergone a colonoscopy in the previous 3-5 years [43]. Flexible sigmoidoscopy has a yield of approximately 9.5% for large polyps and cancer [44]. Similar polyp miss rates have been noted with this procedure [45]. Nonetheless, its use as a stand-alone technique has been hampered by the limited colonic views obtained by the procedure and associated uncertainty over what findings would necessitate proceeding to full colonoscopy [32]. There is considerable debate regarding the benefit of full colonoscopy in reducing mortality from right sided cancer, compared to FS examination of the colon alone [35]. A large Canadian study did not note any reduction in mortality from right-sided CRC after colonoscopy, though the screening colonoscopies were unidentified [46]. By contrast, an examination of 10,124 consecutive screening colonoscopies by Imperiale et al identified 42% of advanced neoplasia proximal to the splenic flexure [47]. Flexible sigmoidoscopy compares favourably with FOBts, when used as a stand-alone screening test, in terms of identification rate of large polyps and neoplasia [39]. A Cochrane systematic review identified a relative risk reduction of 0.85 for FS over FOBt [38], whereas a recent large-scale randomised controlled trial (RCT) of one-off FS as a sole screening tool demonstrated a 33% reduced incidence of CRC and 43% reduced mortality [48], data supported by other large prospective RCTs [49, 50]. Analysis of the optimum cost-efficiency in screening with guaiac FOBt and/or FS has shown the benefit of a one-off FS at age 60, followed by biennial FOBt (+ colonoscopy if FOBt positive) at ages 61-70, with an estimated 22.7% reduction in CRC cases and 33.4% reduced deaths from CRC [51]. As a result, the UK BCSP has plans to offer a one-off FS at age 55 from 2013, in addition to the FOBt +/- colonoscopy already in place [2].

**ENDOSCOPY-RELATED RISK**

Endoscopy itself may be poorly tolerated and has several potentially major dangers, most notably perforation and haemorrhage post-polypectomy. Sedation or general anaesthetic and bowel preparation in at-risk individuals is also a source of risk. Risk of bowel perforation and haemorrhage has been estimated at between 0.1 and 0.25% for perforation and between 0.3% and 2.1% for bleeding [52]. However, such data is extremely variable according to location and study [6]. These dangers are emphasised further when considering the numbers of individuals potentially exposed. For example, using the data produced by the US Multi-Society Task Force Risk, of 157 colonoscopies required to detect 1 cancer at worst this would expose 3.3 patients to perforation for each cancer detected [7]. However, in the UK BCSP, of 36,460 colonoscopies performed August 2006-2009 in the UK, a 0.09% perforation rate was noted, with major or intermediate bleeds noted at 0.13%, despite an approximately 50% polypectomy rate; no fatalities were noted [2, 6]. Several factors might account for regional variations in colonoscopy and FS complications, including the training and experience of the endoscopists, whether or not sedation was routinely used, the nature of sedation or general anaesthesia, the quality of bowel preparation, polypectomy rate and local prevalence of resectable lesions.

**ECONOMIC COSTS OF GASTROINTESTINAL ENDOSCOPY**

A three-round pilot study of screening as part of the UK BCSP identified a calculated cost of £5900 (€70000) per life-year saved [2]. Despite the unquestionable benefit of increased early identification of potential CRC in asymptomatic individuals [51], higher detection rates also mean an increased burden on colonoscopy services [32], though this might be alleviated to some extent by adjustment of the cut-off threshold in the FOBt, as suggested above, or adjustment of the colonoscopy training criteria, such as introducing screening certification as part of general endoscopic training for luminal gastroenterologists. Even a small increase in the positive FOBt rate might contribute to a significant increase in colonoscopic burden. For example, it has been estimated that “a sustained 2.5% positivity rate in an area with average acceptance rates will result in a 25% greater demand for colonoscopy in that screening centre compared with the national average” [32]. Endoscopy-based screening services are expensive to establish and maintain, at approximately £3000 (€3600) per quality-adjusted life-year (QUALY) [51]. Thus any refinement of the screening process might be financially beneficial and, moreover, adjustment of screening criteria would allow improved coordination with local healthcare funding priorities. This might potentially involve a more complex risk stratifying model such as screening moderate risk with CT colonography (CTC, equal in sensitivity and specificity to optical colonoscopy if performed with the latest 3-D technology by specifically-trained radiologists, though with a smaller risk of complications) [14, 15], or a panel of biomarker tests in addition to, or in replacement, of FOBt.

**ADJUVANT SCREENING TECHNOLOGIES**

CT colonography, using the latest techniques, equipment and appropriately trained radiologists, has demonstrated a considerable improvement in sensitivity and specificity over the past 10 years. A 2005 meta-analysis shows sensitivity 85-93% and specificity of 97% for polyps and malignancy >1cm, though considerably less sensitive for smaller lesions [53]. By 2011, a meta-analysis could claim a superior sensitivity of 96.1% for cancer detection using CTC, compared to 94.7% for optical colonoscopy, suggesting diagnostic equivalence [41]; the use of 3-D imaging was noted as particularly beneficial for J Gastrointestin Liver Dis, June 2014 Vol. 23 No 2: 195-202
the identification of early neoplastic change. Such diagnostic accuracy is not universally supported, particularly for lesions <6mm, however there does appear to be a broad consensus of the utility of this tool in screening [40]. The procedure is often touted as less invasive, showing considerably lower risk of perforation (approximately 0.009% in one large multicentre study) [54] and reduced discomfort, despite CO₂ insufflation, compared to optical colonoscopy [55]. Though it must be considered that any polyps detected will require colonoscopic removal and the attendant risk attached to that procedure. For screening programmes specifically, some studies have highlighted the benefit of a potential increase in uptake of screening due to patient preference for this test over colonoscopy [55, 56]; though this is not supported in all studies [57]. Further benefits include the potential for evaluating extra-colonic organs, including staging any identified malignancy, and the possibility of avoiding bowel preparation through the use of faecal tagging [2].

Two major drawbacks of this technique include radiation exposure and the cost of providing the service. A wide range of potential radiation doses have been reported depending on CT protocol used. However, there is a lack of clarity on the oncogenic risk attached to lower dose studies (<100mSv, typical CTC study radiation ranges 4.0-13.2 mSv) in particular, as well as in the role of iatrogenic radiation in sporadic cancer in the general population [58]. As yet, no epidemiological study has proven a link between low dose iatrogenic radiation exposure and risk of malignancy [58]. A recent risk–benefit analysis of CTC in an asymptomatic screening population identified a 0.15% risk of radiation-related malignancy for an average 50 year old undergoing the procedure every 5 years from age 50-80, including follow up scans required to investigate any potential extra-colonic findings. Overall the risk was felt to be justified by the benefits of early identification of malignancy [59]. Further developments in 3-D scanning, CT resolution and faecal tagging may assist with a reduction of associated risks by increasing sensitivity for small adenomas and other dysplastic tissues, thus reducing the number and interval of scans required. Economic cost is the other major hiccup in the use of CTC more generally in population screening for CRC. A 2012 meta-analysis of CTC use in screening identified that key determinants of cost-effectiveness were the threshold for polyp referral for colonoscopic assessment and removal, or the inclusion of extra-colonic findings [60]. Given that the risk of marked dysplasia and malignancy is thought to be less than 1% in polyps <6mm [60], referral of only those polyps greater than this size and in sufficient number would allow for an improvement in cost-effectiveness in line with local screening and healthcare funding priorities. Unfortunately the study was inconclusive as to the overall cost-effectiveness of CTC in a screening population [60]. A hypothetical model comparing 10-yearly CTC with biennial FOBt, 10-yearly FS and colonoscopy in asymptomatic screening population aged 60-69 identified increased cost-effectiveness for CTC over optical colonoscopy, with the optical approach demonstrating an incremental cost per QUALY of £34,002 (£41,100) [61]. Although the above evidence has garnered considerable support from a wide variety of national guidelines as one potential option, it is mostly recommended for those unsuitable for colonoscopy in national screening programmes [26, 62], rather than a stand-alone tool. This is in part due to insufficient evidence as to the exact role in the screening process, given that abnormalities often require colonoscopic evaluation, the associated reduction in mortality and morbidity as well as the relative cost implications of integrating CTC into large-scale programmes. This includes a shift of the burden of screening cost from colonoscopy to radiology services [60]. Further clinical studies are underway to evaluate the potential in this technique [63, 64].

The air-contrast barium enema is another imaging tool used to examine the bowel for neoplasia, especially for peri-surgical examination. It has previously been favoured for imaging the colon due to its high sensitivity for established cancer, low cost and few side effects [65]. However, a 2005 prospective cohort study identified poor overall sensitivity (41%, compared to 55% and 98.7% for CTC and colonoscopy) and specificity (82%, 89% and 99.6%, respectively) for adenomatous lesions >6mm [66]. Although frequently mentioned, the barium enema does not now feature prominently in most population-level CRC screening guidelines.

**FAECAL BIOMARKERS**

The ideal biomarker will identify both high risk adenomas, which require excision, as well as established CRC, while excluding the normal bowel from further examination. It would function as a single “point of care” test which could guide therapeutic colonoscopy with a high degree of sensitivity and specificity, thus providing savings both in terms of risk to the patient and cost to the service provider. A marker correlated with TNM stage would aid scheduling of treatment. Diagnostic biomarkers for CRC are a popular area of research, using faeces as well as breath, blood, urine and tissue, focusing on three main categories of approach: cytogenetic methodology, protein assays and volatile organic metabolites (VOMs).

**Faecal Cytogenetic Biomarkers**

Colonocyte DNA is relatively simple to extract from faeces and has been the most successful basis for biomarker detection published to date. The majority of cytogenetic biomarkers have focused on identifying characteristic genomic and epigenetic changes present in CRC, through isolation and assessment of tumour-related DNA from faeces and blood (serum and plasma). To a lesser extent investigation of miRNA thought to be connected to tumour cells has also borne fruit. Panels of methylated genes such as: APC, ATM, hMLH1, SFRP2, HILTF, MGMT, GSTP1 or VIMENTIN have been frequently examined independently or in combination with mutation markers such as APC, k-ras, p53 and BAT-23, with variable sensitivity and specificity [67].

Two recent meta-analyses have examined the potential for using faecal DNA markers in the diagnosis of CRC [67, 68]. Luo et al used methylation markers alone to calculate a mean sensitivity of 62% and 89% specificity for detection of CRC and 54% and 88% respectively for adenoma [68]. Yang and colleagues examined the literature on methylation and mutation markers in a slightly different way: looking for potential risk stratification. They identified a sensitivity
of 68% and specificity of 93% for CRC and 33% sensitivity and 94% specificity for high risk adenomas but no significant identification of moderate risk subgroups of either [67]. Methylation markers were identified as more sensitive but less specific than mutation markers [67]. The most promising panel of tests shows the utility of a combined approach, measuring BMP3, NDRG4, vimentin and TFP12, with mutant KRAS and α-actin. A blinded, multi-centre case-control study identified 85% of samples with CRC and 54% with adenomas >1cm, to a specificity of 90%. Detection rates did not vary with site of tumour and were greatly increased for larger adenomas (>4cm, 92%) [69]. An assay of faecal methylated VIMENTIN (ColoSure™) has been introduced as a commercial test. Simultaneous measurement of methylated Vimentin and DNA integrity in faecal samples demonstrated 87.5% sensitivity and 82% specificity [70]. However, faecal DNA measurements remain less cost-effective than current population-based screening methods, partly due to high individual cost [71].

MicroRNAs (miRNAs), a putatively more stable corollary of mRNA, are another extractable neoplasia-related stool biomarker. A comprehensive review of the subject has been published recently in this journal [72]. Faecal miRNAs have achieved similar efficacy for immunochromelal FOBts [72]. For example, stool miR-106a demonstrated a sensitivity of 34.2% and specificity of 97.2% which, when combined with an immunological FOBt, improved to 70.9% and 96.3%, respectively [73]. Other reasonable biomarkers include miR-135 (46.2% sensitivity, 95% specificity) [74] and miR-144 (74% sensitivity, 84% specificity) [75]. Again, relative cost implications and the current lack of research in this specific area precludes their use in screening in the short term, while potentially leaving them as an option for future testing, most likely as part of a panel of cytogenetic markers.

**Faecal Protein-based Biomarkers**

The low sensitivity of FOBt has also led to an increased interest in the identification of alternative biomarkers found in stool. Transferrin has been quantified as a representative of faecal haemoglobin, because of its comparatively increased stability in samples. However, even when combined with both immunological and guaiac FOBt, only 76.5% and 88.2% sensitivity, respectively, was achieved for detecting both CRC and pre-cancerous lesions, with a specificity of 64.3% and 48.7%, respectively [73]. In the same sample group, the immunological FOBt achieved 69.4% and 75.5% sensitivity and specificity for identification of both types of lesions combined [28]. Tumour M2-PK is the dimeric form of the M2 isoenzyme of pyruvate kinase, which is thought to be characteristic of tissues which are undergoing neoplastic change [5]. A meta-analysis of faecal M2-PK levels by Tonus et al compared guaiac and immunological FOBt, demonstrating a mean sensitivity of 80.3% with specificity of 95.2% for M2-PK (compared to guaiac FOBt with 13%-50% sensitivity and 7.3%-20% for immunological FOBt) [5]. As might be expected from the nature of the biomarker, M2-PK scored particularly highly when detecting early adenomas, compared to both guaiac FOBt and immunological FOBt [5], though some other studies have not reflected this trend [76]. A further recent meta-analysis summarised with a sensitivity of 79% and specificity of 81% [77].

Measurements of neutrophil-related markers have also proved popular, with studies involving faecal calprotectin, calgranulin B (a heterodimer of calprotectin) and lactoferrin [78-81]. However, such studies have reflected a lack of specificity for colorectal neoplasia, even in comparison to guaiac FOBt, partially due to their strong link with colonic inflammation [82]. Other tumour-related proteins such as minichromosome maintenance protein (MCM2), carcinoembryonic antigen (CEA), decay-accelerating factor (DEA) and clusterin have also been investigated in small-scale studies for potential screening use, with varying sensitivity and specificity [83-86], though as yet none appear to offer considerable improvement over FOBt.

**Faecal Metabolomics**

Techniques which seek to measure the metabolome of the gut have recently garnered interest as a method of characterising the complex interaction between the microbiome and host cells in both disease and health. These approaches can identify metabolic changes associated with different disease states [87, 88]. Volatile organic compounds (VOCs) released from faeces, breath, serum, urine and the tissues themselves can be evaluated as an assessment of the volatile organic metabolome (VOM). The identification of a specific “odour-print” associated with disease as a screening tool either by machine or using the canine nose has demonstrated impressive sensitivity and specificity [89, 90]. Several studies have attempted to correlate VOCs with various colorectal samples. In a broad approach, using an electronic nose, De Meij and colleagues analysed a total of 157 stool samples (40 with CRC, 60 with advanced adenomas and 57 healthy controls), identifying a sensitivity and specificity of 85% and 87%, respectively for CRC, together with those of advanced adenomas, though with reduced sensitivity of 62%, specificity 86% [91]. However, many of the established techniques for VOM measurement in stool remain as “proof of concept” studies and have not yet been validated in large clinical cohorts. For example, Monleon et al explored the constituents of faecal water using an NMR-based approach. Although not specifically geared to establish faecal water analysis as a screening tool, it did identify a significant reduction in short chain fatty acid levels (butyrate and acetate) in CRC patient stool compared to control [92]. Sonoda et al utilised specifically trained dogs to identify the stool of patients with colorectal cancer, with a sensitivity of 97% and specificity of 99% [93]. However, this was examined in only 37 samples and such success has proven difficult to replicate in other studies using different dogs, odour material and other types of cancer [94]. Further studies are required in this area to evaluate the myriad of potential connections between the VOM, as detectable in stool, blood, breath and urine, and colorectal neoplasia.

**CONCLUSIONS**

Many countries maintain successful screening programmes for colorectal cancer. At a population level many of these involve a combination of FOB testing and colonoscopy. However the sensitivity and specificity of current screening modalities remain clinically suboptimal, exposing patients to risk of harm and the screening services to increased cost. No particular
screening methodology has been identified as clearly more cost-effective than any other [95]. The key step in achieving maximum efficiency from population screening appears to be in the uptake of the test. Thus a shift from guaiac FOBt to immunological FOBt, with the associated improvement in acceptability to the patient, appears to be an important initial step, together with improved patient education about the purpose and nature of the screening and increased options for further investigation. However, ideally, a more acceptable and more accurate test would be employed instead or concurrently to reduce the number of colonoscopies required. Increased integration of CTC services into population screening appears to be a potentially promising approach. This could be done by further risk stratification, either through the immunological FOBt itself, through risk modelling for such factors as risk of right sided malignancy or as a method of investigating those “intermediate” risk FOBs which would usually require repeated FOB testing immediately. A low risk individual, positive for FOB, might be offered CTC in preference to colonoscopy. Several stool-based tests appear to have potential for improving diagnostic efficiency. Faecal sDNA panels demonstrate impressive sensitivity and specificity, especially when combined with immunological FOBt. However, sDNA testing remains considerably more expensive than immunological FOBt when used as a screening tool and appears no more acceptable when the practicalities of sampling are taken into consideration. Faecal M2-PK also appears promising, particularly in the detection of early neoplasia, though again, it is more expensive than immunological FOBt and is likely to have a similar uptake from the screening population. Faecal VOM measurement also may have a role to play, although studies have not demonstrated significant validity in large patient groups.

Overall, a multi-layered risk stratification approach, hypothetically integrating FOBt and both serum and faecal biomarkers such as M2-PK and sDNA, to determine effectively who could be offered CT colonography and who ought to proceed straight to optical colonoscopy, could potentially be combined with a risk-prediction algorithm to improve the efficiency of the programme further [96, 97].

Conflicts of interest. The authors have not identified any potential conflict of interest.

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