Review Article

FIT for purpose: enhanced applications for faecal immunochemical tests

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Abstract: Colorectal cancer (CRC) is one of the most prevalent cancers. Early diagnosis has a major impact on survival, and can be achieved with screening programs. CRC screening participation with faecal immunochemical tests (FIT) detects CRC at an earlier and more treatable stage, resulting in a decrease in mortality, and a reduction in incidence through detection and subsequent removal of precursor adenomas. CRC screening, as well as the need for individuals to have ongoing surveillance colonoscopy following diagnosis of neoplasia, results in an increasing burden on colonoscopy resources. This can result in lengthy waiting times for colonoscopy, with a potential consequence being increased stage of disease as well as patient anxiety. These issues associated with FIT programs could be addressed through improving test accuracy in both sensitivity and specificity, as well as tailoring screening to the risk factors of the individual. FIT hemoglobin (Hb) concentrations in combination with clinical risk factors could be used to plan screening intervals as well as triage for diagnostic colonoscopy. Smart use for FIT could also be within symptomatic patients or in the higher risk population with a view to achieving more efficient and cost-effective use of colonoscopy. The evidences underlying these strategies are explored in this review, with a focus on enhanced applications of FIT to reduce the burden on limited colonoscopy resources.

Keywords: Faecal immunochemical test (FIT); colorectal cancer (CRC); advanced neoplasia; hemoglobin (Hb); colonoscopy surveillance

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Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide, with approximately 1.4 million new cases diagnosed and 608,000 deaths per year (1). Despite the high likelihood of cure following quality treatment when diagnosed at an early stage, CRC remains the second leading cause of cancer death globally. Screening aims to reduce CRC incidence and mortality through detection and removal of early stage cancers or precursor adenomas. Globally faecal occult blood tests (FOBT) with either guaiac FOBT (gFOBT) or the newer faecal immunochemical test (FIT) for hemoglobin (Hb) (2) are widely used in CRC screening of average risk populations with positive results triggering colonoscopy.

Screening with gFOBT reduces both incidence and mortality from CRC (3-6), through early detection of neoplasms exhibiting a bleeding phenotype. However technical issues associated with the methodology can result

in both false negative and false positive results. gFOBT detects the presence of heme using an oxidation method, and is therefore susceptible to interference from either intake of anti-oxidants such as vitamin C (increasing risk of a false negative), or intake of heme in red meat or of peroxidase-containing fruits and vegetables (increasing risk of a false positive) (7). In addition, the test is not specific to colonic bleeding, and therefore detected heme can originate from the upper gastrointestinal tract. Accordingly the test has specificity issues as well as limited sensitivity for both CRC (33.3%) and high risk (advanced) colonic adenomas (6.8%) (8). These limitations have prompted many countries to adopt FIT as the CRC screening test for mass population screening where most targeted are of average-risk for CRC. FIT uses antibodies specific for the globin moiety of human Hb. This methodology is sensitive to low concentrations of globin that originate from the colon and is unaffected by medication and diet (9). It is also a consumer preferred test over the gFOBT (10), with this contributed to by the easier sampling technique and the lack of dietary restriction (11). Head-to-head comparison against gFOBT have shown that sensitivity for commonly used FITs were better for both CRC (73.3–87.5%) and advanced adenomas (22.2–42.6%), compared to gFOBT (CRC: 23.0–33.0%; advanced adenomas 6.8–23.0%) (8,12). Recent studies support the role of this technology in early detection of CRC, as well as reducing incidence and mortality from CRC (13-15).

A FIT positive test result is based on the presence of Hb above a set threshold (typically between 15 and 20 µg Hb/g faeces), with its use as a screening modality to determine who should proceed to colonoscopy. An advantage of the FIT is that some FIT brands are able to provide quantitative Hb results, although most countries using FIT for CRC population screening only report qualitative test results even when using a quantitative test. A quantitative result provides the ability for more sophisticated applications and the faecal Hb concentration correlates with pathology in that cancers bleed more than advanced adenomas which bleed more than those with diminutive adenomas and no evidence of pathology (16).

In this review we will discuss how knowledge of Hb concentrations can extend FIT usage, for example in combination with clinical factors or other biomarkers to improve screening efficiency, as well as allowing for efficient and cost-effective management of colonoscopy resources in screening populations. We will also explore some non-traditional uses of FIT, in symptomatic patients or higher risk subgroups.

Improving FIT screening sensitivity

FIT has a high sensitivity for colonic neoplasia (8), but with a specificity of 94% (17) substantial numbers of colonoscopies on FIT positive individuals do not detect neoplasia. Increasing participation in FIT for CRC screening has resulted in longer waiting lists for diagnostic colonoscopy. Australian screening program data from 2006–2009 revealed only 23% of participants had their diagnostic colonoscopy within 30 days (the recommended benchmark at that time) after a positive FIT (18). Delays to diagnostic colonoscopy not only increases severity of pathology outcomes but also increases patient anxiety. Studies indicate that there is a higher likelihood of being diagnosed with stage II CRC after a 7–9-month delay (OR 1.88) (19), and that a delay of 12 months will increase the incidence of all CRC by 4% compared to more timely procedures (20). These data also suggest that delays increase mortality by up to 16% and decrease programmatic cost effectiveness by 9% (20). From a patient perspective, while a positive FIT result increases anxiety, this decreases after colonoscopy. This further supports need for timely diagnostic procedures. Below we discuss use of FIT to triage patients for diagnostic colonoscopy, and how test sensitivity may be improved.

Neoplasia prediction through combining FIT results with clinical data

A number of personal and lifestyle factors are associated with a higher risk of CRC development. It is possible that the knowledge of these could be applied to determine how to prioritise FIT positive individuals for earlier procedures. Stegeman *et al.* combined a number of risk factors with the FIT result including age, gender, smoking status, family history of CRC and calcium intake and reported sensitivity for advanced neoplasia (CRC or advanced adenoma) was better than with FIT alone (22). Another study found a higher risk for advanced neoplasia in individuals with high faecal Hb concentrations, older age, male gender, smoking and metabolic syndrome (23). Further studies are needed to validate these models for clinical triage purposes.

Neoplasia prediction through combining FIT with other biomarkers

Neoplasia detection by FIT relies on lesions shedding blood into the faeces. However, some lesion are more likely to escape detection if they bleed little or not at all. The degree

of bleeding seems to be location and/or histopathology dependent. For instance right sided lesions are less likely to be associated with a positive FIT result compared with left sided lesions (24), due to degradation of Hb during transport along the colon, and serrated adenomas with hypovascularisation and mucous cap also have poor sensitivity with FIT (25). To identify other phenotypes apart from bleeding, there could be value in combining test technologies. There are now data examining outcomes by adding different biomarkers to FIT, either in faeces, or in other body fluid such as blood.

Our group has previously explored the value of blood biomarkers to detect a different pathobiology than that detected by FIT. Circulating tumour DNA (ctDNA) can be detected in the blood stream through assaying for DNA changes specific to CRC such as mutations or methylation. An example of aberrant methylation shown to be related to colorectal neoplasia is in the genes *BCAT1* and *IKZF1* (26). In a prospective study involving 1381 participants undergoing colonoscopy, and who completed both FIT and the methylated *BCAT1/IKZF1* blood test, we found that a blood test for these two genes in combination with the FIT, improved CRC sensitivity to 89% which was greater than either test alone (FIT =79%, blood test =62%) (27). Another study has suggested that combination of a positive FIT result and markers of iron deficient anaemia indicates an increased risk of advanced colorectal neoplasia (28). However including a blood test for iron deficient anaemia did not detect additional cancers compared to FIT alone. A further limitation was that the study did not include menstruating women. Nevertheless this combination of tests might guide triage strategies for those more likely to have advanced neoplasia.

A recent review of different fecal biomarkers assessed in combination with FIT found that the biomarkers based on DNA mutations (p53 and APC), DNA methylation (PHACTR3), and microRNA (miR-106a) expression all improved diagnostic test accuracy for advanced colorectal neoplasia, with sensitivity of 71–81% for the combined test compared to 52% for FIT alone. In contrast biomarkers based on proteins (transferrin, calgranulin C, TIMP-1, peanut agglutinin, calprotectin and M2-PK) did not (29). One combination test that is more advanced with testing is the multitarget fecal DNA test (Cologuard). The DNA test includes assessment of DNA mutation (KRAS), DNA methylation (NDRG4 and BMP3), as well as an immunoassay for Hb (i.e., a FIT). The detection of advanced adenomas and large sessile serrated adenomas was improved in using the combination test (42.4% for both) compared to FIT alone (23.8% and 5.1% respectively) (30). Another study that assessed the combination of FIT with microbiota testing (sequencing the 16S rRNA genes) detected 92% of cancers compared to 75% for FIT alone. In addition the tests each detected distinct small subsets of adenomas (31). However the technical limitations of this work were that the FIT was performed on frozen fecal aliquots which can decrease test sensitivity through reducing fecal Hb concentrations (32). In addition not all samples were collected prior to colonoscopy so it is unclear how practical this approach is at present.

Prior to wide use of the combination options, it is important that they undergo a full evaluation such as that suggested by Pepe (33,34). These include validation of accuracy, and critical evaluation in practice on an intention-to-screen basis. The majority of the novel biomarker tests described have however, only been assessed in single studies, or not in a screening setting. Cost effectiveness is an important consideration with the combination tests as many of these are associated with a reduction in specificity, which will increase the burden on colonoscopy resources. While the multitarget fecal DNA test is now commercially available, its cost effectiveness has been questioned. The point has been made that for the multitarget fecal DNA test to be cost effective it will need to increase screening participation over the current rates in the FIT program alone (35).

Tailoring FIT screening programs to the individual

The technology of many brands of FIT allows Hb concentration to be reported quantitatively. While most diagnostic laboratories follow manufacturers' recommendations for positivity thresholds, with quantitative results it is possible that thresholds can be adjusted to match the desired sensitivity and specificity of a screening activity (9). Possible options to exploit this are described below.

Personalizing FIT screening based on risk factors

As colonoscopy capacity is limited in many countries, there is a need to ensure feasible access and cost-efficient use of this resource. Limiting CRC screening from 50 to 74 y is one approach to maximize the benefits per unit cost. Within this age range it may be possible to pre-select who would benefit most from screening. Identified risk factors for CRC include familial genetic predisposition, previous medical

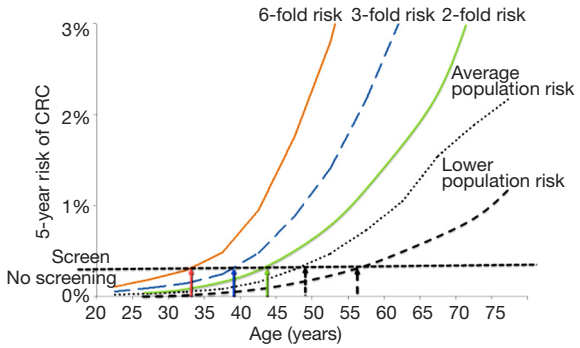

Figure 1 Five-year risk of colorectal cancer (CRC) by age, according to risk group. Risks are estimated from that of the average-risk population. The dotted horizontal line shows the risk at which FIT-screening starts in average risk groups, and where a comparable risk is seen in other risk subgroups. For example, screening would logically start at about age 44 if one is twice the average risk. Figure courtesy of Prof. Mark Jenkins, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Australia.

history and lifestyle factors. Family history can increase an individual's risk of developing CRC up to four-fold (36,37). Of major impact is the increase in incidence of adenomas and polyps with age (38). Gender is also important (39,40), as men are 1.4 times more likely to be diagnosed with CRC compared to women (38). In addition, smoking, alcohol, BMI, physical activity and nutrition have been shown to play a role in development of CRC (41).

Knowledge of these risk factors could be used for better selection in individuals of the age at which FIT screening should commence. Models for risk prediction have included family history of CRC, aspirin use, smoking, vegetable intake, physical activity, BMI, gender, prior colonoscopies and hormone replacement therapy use or estrogen status (42,43). Individuals at elevated risk for CRC according to such a stratification model may start FIT screening at an earlier age than recommended for general population, while those in lower risk subgroup could commence screening at an older age. While the models being developed are promising, these are still under development but there is the tantalising possibility of incorporating multiple environment risk factors, multigenerational family history for CRC, as well as other cancers (44) to enhance the risk stratification and guide screening recommendations. This is illustrated in *Figure 1*, which shows how age of screening could be tailored to clinical risk status for CRC. It demonstrates how if we can determine an individual's risk status for CRC development (compared to the average risk population), we can then recommend the age at which screening should commence (based on setting a threshold for CRC risk at which screening should commence).

Adjusting positivity thresholds to suit the individual

A number of risk factors can also be reflected in the range in FIT positivity reported by different screening programs. We and others have previously shown that faecal Hb concentrations vary by gender, age and deprivation status (24,38,45). Hb concentrations have also been compared between different geographical populations. A large study showed that faecal Hb concentrations were higher in Scotland compared to Taiwan and Italy. This study also demonstrated age and sex differences in faecal Hb (46). Information on the distribution of Hb concentrations within a population may be important to allow screening programs to tailor positivity thresholds. Ignoring the different faecal Hb concentrations between different ages and gender, has implications for the effectiveness of screening in subgroups defined by these demographics. One study has suggested that the FIT positivity threshold can be increased in women under 60 years, which would not affect the cancer detection rate, but would decrease the number of colonoscopies performed by 44.5% (47). By individualizing FIT positivity thresholds, there could also be a reduction in the risk of interval cancers.

Adjusting screening intervals based on Hb concentrations

In addition to the known risk factors that have been discussed above, it appears that the risk of advanced neoplasia at screening may be predicted by FIT results from previous screening episodes. There is a 27% to 35% lower rate of positivity (48-50) if study enrollees have previously undergone screening. This highlights the importance of participation to the success of a population screening program. A higher FIT Hb concentration is also associated with a higher risk of advanced neoplasia (16,51), risk of interval cancer at a future colonoscopy (52), as well as increased mortality for CRC (53). Therefore an individual will have lower risk of advanced neoplasia after previous participation in FIT screening and have a lower fecal Hb concentration.

Screening programs routinely report FIT results in a qualitative fashion, i.e. positive or negative, and around the world, threshold Hb concentrations defined as positive

Table 1 Findings of advanced neoplasia following a negative faecal immunochemical test result

Country/region	Positivity threshold	Age range (years)	Round 1—no detectable Hb	No. AN at follow-up (%)[1]	Round 1—definition of high negative	No. AN at follow-up (%)[1]
Taiwan (57)	20 μg Hb/g faeces	40–69	0 μg Hb/g faeces (n=18,995)	115 (0.6)	16–19.9 μg Hb/g faeces (n=508)	17 (3.3)
Italy (54)	20 μg Hb/g faeces	58–69	0 μg Hb/g faeces (n=73,233)	351 (0.5)	10–19 μg Hb/g faeces (n=3,126)	256 (8.2)
Scotland (58)	80 μg Hb/g faeces	50–74	0 μg Hb/g faeces (n=16,621)	19 (0.1)	60–79.9 μg Hb/g faeces (n=125)	13 (10.4)

[1]No. AN (advanced neoplasia) = advanced adenoma + colorectal cancer, with the percentage calculated of the population in round 1. Hb, hemoglobin.

range from 15 to 80 μg Hb/g faeces. Only individuals with a positive FIT test undergo a colonoscopy, whereas participants with a negative FIT result are recommended to repeat screening (in typically 1–2 years), regardless of the actual Hb concentration. Recent studies in large screening cohorts show that values, even if below the positivity threshold, are predictive of future colorectal neoplasia (54-58). Some of these studies are summarised in *Table 1*.

One of the first studies to describe this was performed in Taiwan. They analysed data from 44,324 FIT negative participants (negative value defined as less than 20 μg Hb/g faeces) from the community screening program. They showed that the prevalence of advanced neoplasia was higher in the individuals who had a Hb concentration at 16.0–19.9 μg Hb/g faeces at the previous screening round (just below the positivity threshold of 20 μg Hb/g faeces), compared to those with a lower initial Hb concentration, with an adjusted hazard ratio for advanced neoplasia of 3.41 (relative to participants with 0.2–3.9 μg Hb/g faeces) (57). A second study by the same group following up 54,921 FIT participants showed an association between baseline Hb concentration and risk of neoplasia, with the prediction based on faecal Hb concentration superior to that using a model based on conventional risk factors (56).

Similar findings were reported from a pilot study in Italy with 118,723 participants who had a negative FIT result. The prevalence of advanced neoplasia was highest following a faecal Hb concentration of 10–19 μg Hb/g faeces (where the positivity threshold was 20 μg Hb/g faeces) with an incidence of 8.2% compared to 0.5% following a FIT result of 0 μg Hb/g faeces (54). Consistent with this are data from the Scottish program where a higher FIT positivity threshold is applied (80 μg Hb/g faeces). 37,780 participants with negative results were assessed for outcomes at the next screening round. Of those that were FIT positive in the subsequent round, the odds ratio for advanced neoplasia was 14.3 (95% CI: 8.9–23.1) for those with a baseline FIT concentration of 20–39.9 μg Hb/g faeces, and 38.0 (95% CI: 20.2–71.2) for those with a baseline FIT concentration of 60–79.9 μg Hb/g faeces, relative to those with a baseline of less than 20 μg Hb/g faeces (58).

These findings were also assessed over four rounds of FIT screening in the Dutch screening program and also included CRC diagnosed outside of the program (55). Using data from 7,663 FIT negative (below 10 μg Hb/g faeces) participants, individuals with a baseline Hb concentration of 8–10 μg Hb/g faeces had a higher incidence of advanced neoplasia than the participants with a baseline FIT result of 0 μg Hb/g faeces (hazard ratio of 8.2). Consecutive high concentration negative FITs were also predictive of future advanced neoplasia risk—participants with two consecutive FIT concentrations of 8 μg Hb/g faeces had a 14-fold increased risk compared with those individuals with FIT values of 0 μg Hb/g faeces.

Despite each study using country-specific definitions of a negative FIT result, the data support the contention that faecal Hb is a strong predictor of future risk of neoplasia. The reason these concentrations are associated with increased risk is because early lesions with low levels of bleeding were missed because they were not colonoscoped. At a later time lesions become evident due to progressively advancing neoplasia resulting in higher faecal Hb concentration. This information could be used to improve the cost effectiveness of screening programs by extending the screening intervals for those with a low negative and increasing the frequency for those with a high negative result. Quantitative FIT results could therefore be applied to tailor screening intervals.

Reducing burden on endoscopy resources

Following a positive FIT, participants are advised to have further investigation with colonoscopy. FIT positivity rates thus have a direct impact on colonoscopy workload, as well as increasing demand for surgical, pathology and radiology services. Continued surveillance of FIT positive patients found to have neoplasia or a family history of CRC further stretches the endoscopy workloads and waiting times. In 2005, 44.3% of colonoscopies in the United States were performed for surveillance (59). Similarly the proportion of colonoscopies done for surveillance was 33.9% in the Netherlands (60). A review in 2010 of 17 countries showed that many countries already have difficulties meeting increasing endoscopy demand, without the addition of diagnostic colonoscopy following a positive FIT, which will further increase demand, resulting in increased waiting times for higher-risk and symptomatic patients (61). One approach to optimize colonoscopy utilisation would be to use FIT to triage symptomatic patients or postpone surveillance colonoscopies as detailed below.

Matching positivity rates to colonoscopy capacity

Quantitative FIT in screening programs allow thresholds for a positive and hence colonoscopy workload to be adjusted to match the capacity of the endoscopy services (9). The Netherlands, Scotland and New Zealand are examples of countries where this has been done. Scotland has opted for a higher FIT positivity threshold (80 µg Hb/g faeces) to match the positivity rate (approximately 2.4%) of the gFOBT originally used in the national screening program (62). The Netherlands started screening with a positivity threshold of 15 µg Hb/g faeces, but increased this to 47 µg Hb/g faeces when high colonoscopy demand occurred after the FIT results returned higher than expected positivity (13.4% *vs.* 6.4%) and participation rates (4.0% *vs.* 2.7%) (63). Similarly, the New Zealand CRC screening program originally set a FIT positivity threshold of 15 µg Hb/g faeces in a pilot program, but have increased this to 40 µg Hb/g faeces for the full program to manage colonoscopy demand (64). It needs to be recognized that increasing the FIT positivity threshold has the benefit of higher specificity, at the cost of a lower sensitivity, although the improvement in sensitivity with a lower threshold mainly relates to adenoma detection rather than cancer (65,66).

Alternatively, FIT positivity thresholds could be lowered, with the screening interval extended. This has been modelled using data from the Dutch screening program (67), with the standard scenario of a FIT positivity threshold of 10 µg Hb/g faeces and biennial screening compared to a hypothetical scenario with a single round of screening and lower positivity thresholds. It was reported that the diagnostic yield of FIT with advanced neoplasia with the altered scenario was similar to the standard screening strategy, which reduces the number of screening rounds needed. This however was not the case when modelled using data from the Scottish screening program (68), which reported that there would be an overall increase in the incidence of interval cancers. This shows that further studies are needed in this area, and results may be program specific.

Use of FIT to triage symptomatic patients

The longer waiting lists for colonoscopy have become a problem in many countries and have led to an urgent need to effectively prioritize procedures. For symptomatic patients, the UK has now incorporated FIT into the NICE guidelines (69) based on the assumption of a low risk of CRC or inflammatory bowel disease associated with undetectable faecal Hb. As symptoms such as change in bowel habits, abdominal pain, anaemia and weight loss have poor clinical sensitivity for CRC (but are common in non-neoplastic gastrointestinal illnesses), FIT can be used to guide decisions to either support or reject the need for colonoscopy. For example it was shown that symptomatic patients with a faecal Hb concentration <10 µg Hb/g faeces had a negative predictive value of 100% for CRC and 94.4% for advanced adenoma (70) suggesting the test could be used to rule-out colorectal neoplasia. Interestingly faecal Hb concentration did not correlate well with clinical symptoms highlighting the non-specific nature of the latter (70). This was supported by a study that concluded that FIT had a higher diagnostic accuracy for significant colorectal disease compared with the NICE guidelines (71). Another study showed that a combination of FIT result, age and gender, and symptoms combined into a single model ruled out CRC in symptomatic patients with the lowest risk score (72). A further study suggested the use of a positive FIT as a rule-in test, where a positive FIT had a significantly higher sensitivity for CRC than the then current NICE guidelines (73). There is an extensive review on this area provided by Steele and Fraser [2018] (74), with the studies described demonstrating innovative clinical application of FIT in the primary care setting to determine which patients could benefit from colonoscopy.

Reducing the number of surveillance colonoscopies in increased risk individuals

Surveillance is recommended for asymptomatic individuals at higher risk for CRC, with colonoscopy being the recommended method. Family history of CRC as well as a personal history of adenoma can increase an individual's risk of developing CRC (36,37,75). Colonoscopy at regular intervals (generally every 3–5 years except in familial syndromes) for these patients is generally performed until they reach an age where surveillance might no longer be considered appropriate. The competing strategies to screen for CRC, whether it be in average risk or high risk subgroups, are invasive and expensive tests such as colonoscopy or more frequent but less invasive and cheaper alternatives typified by FIT. The risk benefit and cost outcomes of these approaches remains unclear. It may be possible for FIT to guide optimal surveillance intervals, which needs to be a balance between preventing interval cancers and avoiding unnecessary procedures.

Despite surveillance, interval cancers are reported to occur after 1.5% of such surveillance colonoscopies (76). As FIT is sensitive for bleeding neoplasia, testing with FIT post-colonoscopy might detect missed lesions as well as rapidly developing lesions. One such investigation showed that FIT between surveillance colonoscopies resulted in detection of additional significant pathology, with detection earlier than would otherwise have occurred (77). Quintero *et al.* (78) conducted a randomised trial to compare the efficacy of annual FIT versus one-time colonoscopy in people with a significant family history of CRC. Performing annual FIT for three years was equivalent to one colonoscopy, but the number of procedures needed to detect one advanced neoplasia was dramatically reduced (4 in the FIT screening group compared to 18 in the colonoscopy group). This agrees with earlier findings that FIT in high risk patients (either family history or personal history of neoplasia) has a high sensitivity for advanced neoplasia with FIT detecting 100% of CRC and potentially avoiding colonoscopy in 84.6% of patients (79).

While colonoscopy can prevent cancer development through the removal of pre-cancerous adenomas, these procedures involve a certain level of risk. A recent audit of colonoscopies associated with positive FITs in the Swedish screening program found complications in 1% of procedures with an incidence of perforation reported to be 0.1% after a diagnostic colonoscopy and 0.25% after polypectomy (80). Reducing the number of low yield procedures is therefore attractive and the acceptable accuracy of FIT in the high risk population suggests a role in this setting to better manage colonoscopy surveillance workloads.

It is probable that multiple rounds of FIT will be needed to ensure high neoplasia detection rates in the high risk population as well as confidence in delay of colonoscopy with repeated negatives or low haemoglobin concentrations. Our own work showed that multiple rounds of FIT sampling aided the detection of advanced neoplasia, with repeated testing resulting in an increase of sensitivity (77). With simulation of multiple screening rounds sensitivity for advanced adenoma could reach 81% after five screening rounds (81). Conversely, risk of advanced neoplasia decreases with multiple rounds of negative FIT. Our preliminary studies have shown three or more negative FITs resulted in a 60–70% lower risk of advanced neoplasia at surveillance colonoscopy when compared to one negative FIT (82). FIT also appears to be cost effective. FIT saved 45% of colonoscopies and was associated with a lower rate of complications compared to 5 yearly colonoscopy (83). Another simulation showed that FIT screening without surveillance reduced mortality from CRC by 50.4% compared to surveillance alone (84). The use of FIT in surveillance for high-risk individuals could therefore reduce the number of colonoscopies, as well as risk to patient, in a cost effective manner. As FIT appears to be as sensitive as colonoscopy for advanced neoplasia, FIT screening should be considered for high risk individuals when colonoscopy capacity is limited.

Conclusions

Optimizing healthcare practices is needed to ensure the best use of resources in the global prevention of CRC. Available data indicate that in those at average risk, the higher the baseline FIT Hb concentration, the greater the risk for a future finding of advanced colorectal neoplasia, even when the FIT result has not triggered colonoscopic intervention. Less frequent screening of individuals at low risk with a very low faecal Hb concentration might be justifiable. Conversely, those with qualitatively negative FIT but whose actual Hb concentration is close to the positivity threshold, might warrant a closer and more intensive follow-up regimen. Further individualization of screening programs and the age at which they commence may also be adjusted according to FIT concentrations but also according to other genetic or lifestyle risk factors. Emerging data also indicate that testing with FIT is likely to provide benefit

for people who are above-average risk for CRC, by reducing the frequency of surveillance colonoscopies. The use of innovative applications with FIT is likely to be a key strategy in the tailoring of CRC screening programs, whether targeting average-risk or higher-risk individuals, as well maximizing the most cost-effective and efficient use of limited endoscopy resources.

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