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Review Article

Towards risk-stratified colorectal cancer screening. Adding risk factors to the fecal immunochemical test: Evidence, evolution and expectations

Wessel van de Veerdonk[a,*], Sarah Hoeck[a,b], Marc Peeters[c,d], Guido Van Hal[a,b]

[a] Faculty of Medicine and Health Sciences, Department of Social Epidemiology and Health Policy (SEHPO), University of Antwerp, Belgium
[b] Centre for Cancer Detection, Bruges, Antwerp, Belgium
[c] Department of Oncology, Antwerp University Hospital, Antwerp, Belgium
[d] Molecular Imaging, Pathology, Radiotherapy & Oncology (MIPRO), University of Antwerp, Belgium

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ABSTRACT

With increasing incidence and mortality, colorectal cancer (CRC) is a growing health problem worldwide. An effective way to address CRC is by screening for fecal (occult) blood by the fecal immunochemical test (FIT). However, there is room for improvement since precursor lesions and CRC bleed intermittent and can therefore be missed by the FIT (false negatives) or, the detected blood did not result from precursor lesions or CRC (false positives).

This review provides the latest evidence on risk prediction models using FIT combined with additional risk factors before colonoscopy, which risk factors to include and if these models will better discriminate between normal findings and CRC compared to the FIT-only.

Many prediction models are known for CRC, but compared to the FIT, these are less effective in detecting CRC. The literature search resulted in 645 titles where 11 papers matched the inclusion criteria and were analyzed. Comparing the FIT-only with the risk prediction models for detecting CRC resulted in a significantly increased discrimination for the models. In addition, 2 different risk-stratification categories before colonoscopy were distinguished, namely the 1-model approach which combined risk factors with FIT results in a prediction model while the 2 step approach used risk factors apart from the FIT. Finally, combining FIT with CRC risk factors by means of a model before colonoscopy seems effective regarding discriminative power, however, more research is needed for validation combined with transparent and standardized reporting to improve quality assessment, for which suggestions are reported in this study.

1. Introduction

In 2018, it is estimated that 1,849,518 new colorectal cancer (CRC) cases and 880,792 CRC deaths will occur worldwide(Bray et al., n.d.). Between 2012 and 2018, both the incidence and mortality for CRC increased. To slow the growing trend of CRC incidence and mortality, CRC screening is viewed as the most (cost-)effective approach (Lansdorp-Vogelaar et al., 2011; Patel and Kilgore, 2015) considering that most CRCs develop from polyps and precursor lesions over the course of several years(American Cancer Society, 2018a) and are therefore particularly suitable for early detection. This will be essential as CRC continues to be an important health problem because of the expected increase of CRC cases in the near future.

The risks and benefits of different CRC screening methods vary based on several quality indicators, which resulted in multiple recommendations of the US Preventive Services Task Force(U. S. Preventive Services Task Force, 2016) and the American Cancer Society (American Cancer Society, 2018b) regarding CRC screening approaches. The screening approach that will be considered in this paper, is the fecal immunochemical test for hemoglobin (FIT) followed by a diagnostic colonoscopy (when FIT is positive). The rationale for this choice is that there is a worldwide shift towards using stool based screening compared to other screening approaches(Schreuders et al., 2015), the FIT is well accepted by the target population compared to other approaches(Inadomi et al., 2012; Navarro et al., 2017) and is cost effective(Murphy et al., 2017; Wilschut et al., 2011).

Furthermore, when comparing the 2 most common approaches (FIT and colonoscopy), there is no superior approach due to variable results which cannot be directly compared and a definitive answer will take at least 3 more years from head-to-head randomized controlled trials (Robertson et al., 2015). Currently, the advanced adenoma detection rate of primary colonoscopy is significantly higher compared to the FIT

* Corresponding author at: University of Antwerp, CDE, D.R.226, Universiteitsplein 1, 2610 Antwerp, Belgium.
E-mail address: Wessel.vandeVeerdonk@uantwerpen.be (W. van de Veerdonk).

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(Quintero et al., 2012). In contrast, FIT participation is significantly higher compared to colonoscopy(Inadomi et al., 2012; Quintero et al., 2012) and colonoscopy is associated with several complications such as perforation, infection and bleeding(Fisher et al., 2011). Considering the 4.5% lifetime risk of CRC(American Cancer Society, 2018c) and that not everyone bears the same CRC risk, it can be argued if all participants benefit from colonoscopy(Wang et al., 2018). Besides, for many countries colonoscopies are burdensome on the healthcare system, specifically, the costs and (limited) capacities of colonoscopy services.

Dividing participants based on the amount of blood found in the stool by FIT, creates more certainty of finding precursor lesions and CRC in a subsequent colonoscopy. Therefore, FIT is ideally positioned to be considered in a prediction model together with other established CRC risk factors. This approach could potentially better discriminate between participants with a normal result, precursor lesions and CRC. Lately, evidence is expanding towards improving CRC screening by using additional risk factors for stratification and using FIT's full quantitative potential. This could increase flexibility and accuracy of the screening without crude increases of the FIT positivity threshold through improved risk prediction before colonoscopy.

This review provides the latest evidence on prediction models including FIT combined with additional risk factors before colonoscopy, which risk factors to include and if these models will better discriminate between normal findings and CRC compared to the FIT-only. While this review is primarily intended for researchers with an interest in novel cancer screening initiatives, it can also help clinicians and health policy experts to gain awareness of the potential of this approach and when effective, provide guidance towards a more efficient and effective use of the FIT. Based on the latest evidence, obstacles and challenges of CRC screening by the FIT in combination with validated risk factors for detecting precursor lesions and CRC are illustrated.

1.1. Methods section

The literature search (Fig. 1) was performed on 17.10.2018 in both PubMed and Web of Science (WOS). The publication date range was set at 1990.01.01 to 2018.10.12 with the search terms: risk prediction model OR stratification AND colorectal cancer screening (PubMed); risk prediction model AND colorectal cancer screening (WOS). The inclusion criteria were papers in English, asymptomatic people who underwent a FIT (irrespective of the brand, cut-off value or specific target age) along with the consideration of additional validated risk factors (such as BMI, smoking status and family history of CRC) before a colonoscopy. Considered study designs are retrospective, cross-sectional and prospective, based on a (pilot) population-based screening program or hospital-based study. These general inclusion criteria were used because of the variability in CRC screening regarding the used tests, target populations, positivity thresholds, follow-up intervals and reporting. Furthermore, a *P*-value below 0.05 is considered significant.

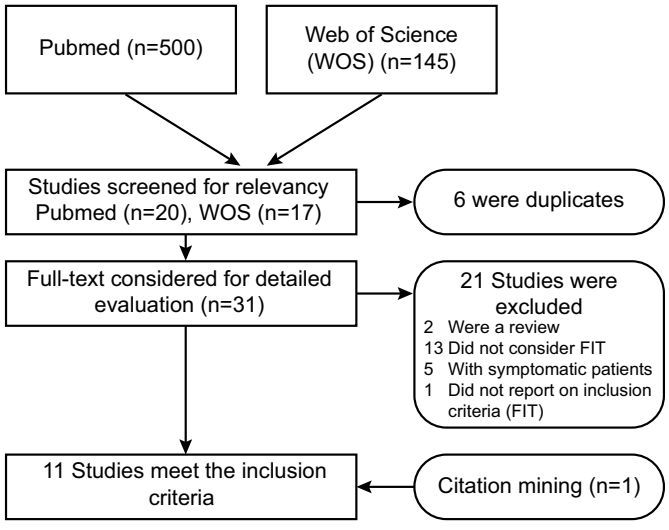

Fig. 1. Flowchart of literature search strategy.

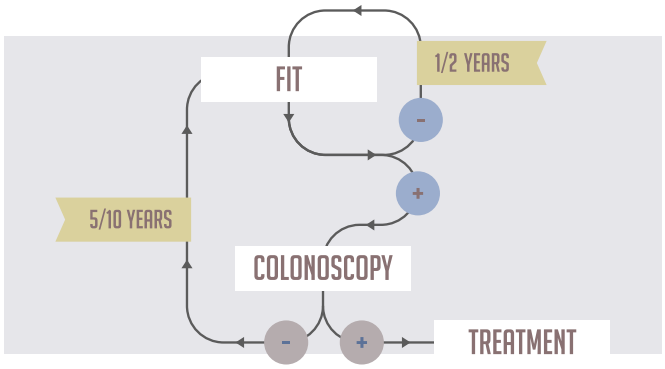

Fig. 2. The CRC screening process based on a predefined target population (e.g. asymptomatic, 50–74 years old).
1/2 = Internationally used FIT screening interval (years). 5/10 = Internationally used FIT screening exclusion criteria, because of a negative colonoscopy (years).

2. FIT basics

The FIT (followed-up by a colonoscopy) is commonly used to screen asymptomatic persons in a population-based CRC screening program based on a target group (e.g. aged 50–74) to detect precursor lesions and CRC in an early stage with the rationale to start treatment before symptoms occur and reduce CRC related mortality (Fig. 2). The FIT is no diagnostic test but a tool to indicate risk for detecting precursor lesions and CRC as established by the amount of hemoglobin detected in the stool(Allison et al., 2014). The FIT result is not just positive or negative but rather a specific amount of hemoglobin, for example between 0 μgHB/g and 200 μgHB/g depending on the FIT manufacturer. The definition of a positive or negative FIT is decided by the country's preferences (oftentimes not recommended by the manufacturer), and because of this, multiple hemoglobin positivity thresholds are used that influence the FIT positivity rate and accuracy accordingly. With a positive FIT (≥threshold), the participant is advised to undergo a colonoscopy, while with a negative FIT (< threshold), participants are considered at less risk for precursor lesions and CRC and are re-invited for FIT with a annually or biennially screening interval(Schreuders et al., 2015).

Evidence shows that a lower FIT positivity threshold such as 15 μgHB/g or 20 μgHB/g provides the best combination of sensitivity and specificity for detecting CRC (93% and 91% or 89% and 91%, respectively)(Katsoula et al., 2017; Lee et al., 2014). These lower thresholds are associated with a higher FIT positivity rate which is burdensome for the colonoscopy service(Toes-Zoutendijk et al., 2017), causing problems to cope with this situation for many countries. For example, if Thailand would use a 10 μgHB/g FIT threshold for screening people aged 50–74, this would result in 1.2 million participants with a positive FIT who are recommended to undergo a colonoscopy, while only 1000 gastrointestinal endoscopists are working in the country who can handle < 200,000 colonoscopies a year(Aniwan et al., 2015). Balance is sought between (limited) resources, high participation rates and large populations by increasing the FIT positivity threshold. Examples are the Netherlands in 2014 (15μgHB/g to 47μgHB/g)(Toes-Zoutendijk et al., 2017) or Scotland in 2017 that started at a higher FIT positivity threshold to begin with (80 μgHb/g)(NHS Scotland, 2017).

Using the quantitative FIT has the potential to improve the population-based CRC screening program. One of these improvements could

be to decrease the number of negative colonoscopies after a positive FIT (false positive for neoplasia). Multiple countries increased their FIT positivity threshold to reduce these false positive results, but as a result created an inversely proportional relationship between a decreasing sensitivity and an increasing specificity for advanced neoplasia (advanced adenoma and CRC) as clearly shown for England by Cooper et al. (2017)(Cooper et al., 2017). Some precursor lesions and CRC will be missed due to this approach and may be detected in consecutive screening rounds in a similar or more advanced stage or will unfold in interval cancers and thus be detected in between screening rounds. Instead of an increased FIT threshold, alternatives are in development that might enhance diagnostic performance of FIT.

2.1. Possibilities with the FIT

Seeing that the FITs used in population-based screening programs are oftentimes quantitative and that each participant has its own specific FIT result and not just a positive or negative result, opens opportunities for risk modelling. At this moment, FIT results are mostly dichotomized by the screening programs while it is known that higher FIT results are associated with increased risk of precursor lesions and CRC. Additionally, best practice is to use continuous variables as such, since by categorizing them (in certain groups) individual information is lost as results become standardized for all the participants in this group (Moons et al., 2015). Using the FIT in a continuous manner would be most obvious in the context of a risk prediction model, since these models can harness the full potential of the quantitative FIT to predict a normal outcome, precursor lesions or CRC. Incorporating other CRC risk factors in such a model could lead to possibilities of assigning CRC risk to a participant on an individual or record level and recommend colonoscopy follow-up based on risk-stratification. The terminology used regarding the modelling and stratification is shown in Table 1.

3. CRC risk factors

Currently, the CRC screening target population is selected based on age, where the selected age range is considered 'at average risk for CRC' due to guidelines and preferences of the country. However, evidence suggests that average risk participants consist out of low to high CRC risk participants based on a simple addition of risk factors(Cooper et al., 2017; Auge et al., 2014; Stegeman et al., 2014; van de Veerdonk et al., 2018). Moreover, low risk participants are more likely to undergo a negative colonoscopy after a positive FIT(van de Veerdonk et al., 2018). This section elaborates on the question: 'How are CRC risk factors currently used and which ones should be included in a prediction model, based on the evidence?'

3.1. Gender

When it comes to the differences in CRC risk, gender is one of the best described variables in current literature as demonstrated by the prediction models considering FIT, where gender is used as a risk factor in 10 out of the 11 studies(Aniwan et al., 2015; Cooper et al., 2017; Auge et al., 2014; Stegeman et al., 2014; van de Veerdonk et al., 2018; Chiu et al., 2016; Jung et al., 2018a; Jung et al., 2018b; Li et al., 2018; Park et al., 2018) and for 1 study, gender is considered independently of the model(Knudsen et al., 2016) as shown in Table 3. A significant association was reported between CRC and gender by 7 studies, where the risk of detecting CRC was higher in males compared to females by an odds ratio range of 1.43–2.18 (Aniwan et al., 2015; Cooper et al., 2017; Auge et al., 2014; van de Veerdonk et al., 2018; Jung et al., 2018b; Li et al., 2018; Park et al., 2018). Additionally, 2 studies used the determinant gender in a validated risk score which assigned risk to men instead of women(Chiu et al., 2016; Jung et al., 2018a). In contrast, 1 study found no significant association between gender and the detection of CRC(Stegeman et al., 2014) and for another study the results to evaluate gender were not reported(Knudsen et al., 2016). Next to the included studies that consider gender together with FIT, gender is considered a clear CRC risk factor (by meta-analyses) across all age groups(Cooper et al., 2017; Auge et al., 2014; Stegeman et al., 2014; van de Veerdonk et al., 2018; Nguyen et al., 2009). While these clear risk differences exist, the same FIT positivity threshold and age ranges are being used for gender in CRC screening.

A recent study illustrated the effect of gender-stratification in FIT screening on the detection and miss rates of advanced neoplasia (Grobbee et al., 2017a) where more advanced neoplasia was both detected and missed in men compared to women. Gender-stratified FIT thresholds such as lowering the FIT positivity threshold in women caused a similar proportional sensitivity for advanced neoplasia in both genders, although, it also resulted in a higher rate of false-positive tests in women. In contrast, lowering the FIT positivity threshold in men led to a similar miss rate in terms of absolute numbers, and to a similar positive predictive value in both genders, however, this also resulted in decreased sensitivity and detection rates for women(Grobbee et al., 2017a). Another study, suggested to lower the target age for men since women reach the same risk as men at an older age(Brenner et al., 2007). To sum up, adapting the FIT positivity threshold or target age based on gender could bring the risk differences between gender closer together in terms of sensitivity or miss rates(Grobbee et al., 2017a) at the expense of increasing false-positive tests or decreased sensitivity and detection rates for women. By stratifying the risk factor gender there seems to be no obvious improvement.

3.2. Age

In general, age is considered a CRC risk factor since increasing age is associated with CRC as shown in the included risk prediction models. 10 out of the 11 studies used age in their models(Aniwan et al., 2015; Cooper et al., 2017; Auge et al., 2014; Stegeman et al., 2014; van de Veerdonk et al., 2018; Chiu et al., 2016; Jung et al., 2018a; Jung et al., 2018b; Li et al., 2018; Park et al., 2018) and 1 study used age independently of the model(Knudsen et al., 2016). 6 out of the 11 studies showed that increasing age is significantly associated with CRC(Aniwan et al., 2015; Auge et al., 2014; Stegeman et al., 2014; van de Veerdonk et al., 2018; Jung et al., 2018b; Park et al., 2018). In addition, 2 studies used age in a risk score(Chiu et al., 2016; Jung et al., 2018a), 1 study did not reach significance(Cooper et al., 2017) and 2 studies reported results that could not be used for evaluation(Li et al., 2018; Knudsen et al., 2016) Evaluating the strength of the association was hindered by variation in reporting, for example, the categorized age variable generally led to higher odds ratios compared to the continuous age variables. Next to this disadvantage, there was still a clear trend between

Table 1
Terminology used throughout the study.

Stratification	Outcomes are shown between different strata of a specified variable. *For example, if a large difference in CRC detection is observed between genders, it is appropriate to report these results in the strata male and female.*
Risk prediction models	Risk prediction models calculate the risk estimate that an individual with a given set of risk factors will experience a certain health outcome. *For example, the CRC probability of a male, aged 73, currently smoking with a BMI of 30 is 'X'%.*
Risk-stratification	The process of separating populations into risk groups such as low-risk, average-risk or high-risk, which is based on a risk prediction model that assigns a specific risk estimate to a participant's profile.

increasing age and CRC. Currently, age is only used for determining the screening target population, where the predictive power of increasing age on CRC is disregarded.

3.3. Family history of colorectal cancer

Regarding the family history of colorectal cancer (FHCRC), there is clear evidence from risk factor studies that FHCRC is a CRC risk factor (Johns and Houlston, 2001; Johnson et al., 2013). FHCRC was included in 6 out of the 11 models(Aniwan et al., 2015; Stegeman et al., 2014; Chiu et al., 2016; Jung et al., 2018a; Jung et al., 2018b; Li et al., 2018), although only 1 study found a significant association between the number of relatives with CRC and detecting CRC(Stegeman et al., 2014). 2 other models used the FHCRC variable in a risk score and assigned risk to FHCRC(Chiu et al., 2016; Jung et al., 2018a), 2 more models did not reach significance(Aniwan et al., 2015; Jung et al., 2018b) and 1 model did not report on the significance of the association (Li et al., 2018). FHCRC was used in a model by either a risk score, as a binary variable or as a continuous variable by the number of relatives with FHCRC. In practice, when sending a FIT to the eligible target population, oftentimes nothing is known about their FHCRC. Therefore, screening participants are informed that FIT is not recommended when FHCRC is present and that they should discuss this with their general practitioner. A previous study reported a reduction of 40% additional deaths if these people did not perform a stool test but rather a colonoscopy(Goede et al., 2015). Theoretically, FHCRC can be incorporated in a prediction model with FIT, although practically this is unlikely since multiple recommendations advise that these people should be followed-up by colonoscopy and not by FIT, resulting in exclusion of these people from FIT screening(Leddin et al., 2018; Schoenfeld, 2018).

3.4. The quantitative FIT result

4 out of the 11 studies (Cooper et al., 2017; Auge et al., 2014; Stegeman et al., 2014; van de Veerdonk et al., 2018) used the FIT in a prediction model and of these, 3 out of the 11 used the FIT as a continuous variable while other studies used some form of categorized FIT(Cooper et al., 2017; Stegeman et al., 2014; van de Veerdonk et al., 2018). These 3 models reported that increasing FIT results were significantly associated with precursor lesions and/or CRC and were the most important predictor in the model(Cooper et al., 2017; Stegeman et al., 2014; van de Veerdonk et al., 2018). Although some variation in reporting was present, large risk differences were obtained by these models, from a significant odds ratio increase of 1.434 per 1 μgHB/g unit increase in FIT (starting from 20μgHB/g to 200μgHB/g) result (Cooper et al., 2017) to a significant odds ratio of 71.2 when comparing the lowest and highest result of FIT(Stegeman et al., 2014). In addition, multiple studies showed an association between increasing quantitative FIT results and more severe colonoscopy findings (Fig. 3)(Auge et al., 2014; van de Veerdonk et al., 2018; Chen et al., 2011).

3.5. Lifestyle factors

7 out of the 11 models included lifestyle factors in this study, most commonly BMI and/or smoking. Smoking was evaluated by the reported odds ratios and was clearly associated with CRC since 4 out of the 7 studies showed significant odds ratios (1.55 to 2.38)(Aniwan et al., 2015; Stegeman et al., 2014; Park et al., 2018; Knudsen et al., 2016), 2 studies used smoking in a risk score(Chiu et al., 2016; Jung et al., 2018a) and 1 study did not reach significance(Jung et al., 2018b). BMI was reported by 3 out of the 7[30, 32, 33] studies of which 2 showed a positive significant association between higher BMI and CRC (odds ratios 1.32 and 1.47)(Park et al., 2018; Knudsen et al., 2016) and 1 was not significant(Jung et al., 2018b). In addition, Knudsen et al. (2016) showed that moderate alcohol consumption was inversely significantly associated with CRC (odds ratio 0.53). All these findings are in line with the literature(Johnson et al., 2013; Moghaddam et al., 2007). More lifestyle related risk factors for CRC could be considered, such as physical activity, the consumption of red meat, fruits and vegetables (Johnson et al., 2013; Chan et al., 2011; Macrae, 2018), as these are associated with CRC but not addressed in the 11 studies.

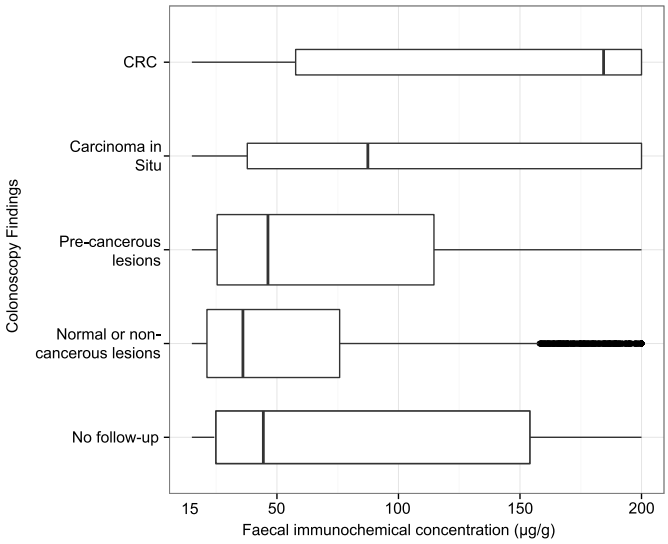

Fig. 3. Box and whisker plots of the difference between colonoscopy findings and FIT results. Significant pairwise differences ($P < .001$) and a difference of $P < .001$ between colonoscopy findings.
Adapted from van de Veerdonk, et al. *Cancer Epidemiology* 2018; 56: 90–96, with permission from Elsevier(van de Veerdonk et al., 2018).

3.6. Risk factors to incorporate in the prediction model with FIT

Considering how risk factors are obtained is important to answer the question which risk factors should be included in a prediction model with FIT. Theoretically, every significantly associated validated CRC risk factor could be included in a prediction model. But practically, within a FIT screening program only a few routinely obtained reliable variables are available, such as age, gender, FIT results and prior screening results which are currently not actively considered as risk factors for predictive purposes in most countries. This means that alternative CRC risk factors should be obtained by other means, which is usually done by a questionnaire or by linking an additional database. The main disadvantages of a questionnaire within a screening program is the risk of recall bias, selection bias (selective group that fills out the questionnaire), social desirability bias and the significant reduction of screening participation(Watson et al., 2013). Therefore, it is recommended to incorporate routinely available variables in a prediction model as a starting point and when possible (in a way with minimal bias and minimal participation loss) add risk factors to the model.

4. Risk prediction models

In this section, the question is addressed if risk prediction models better distinguish normal findings from CRC compared to FIT-only.

There is plenty of evidence concerning risk prediction models for CRC(Ma and Ladabaum, 2014; Usher-Smith et al., 2016; Win et al., 2012; Wong et al., 2015; Usher-Smith et al., 2018; Smith et al., 2018), however seldom in the context of a population-based CRC screening program causing FIT to be not included. Either way, considering risk prediction models without FIT as a screening approach adds little value, since most of these models demonstrate relatively weak discriminatory power and no generalisability(Ma and Ladabaum, 2014). For this reason, studies started incorporating risk factors associated with precursor lesions and CRC together with the FIT. The results of these

studies (Table 3) were most promising as the risk differences for detecting precursor lesions and CRC became even more notable. For example, based on a population-based FIT screening program in Belgium a multinomial prediction model estimated that men aged 74 with a FIT result of ≥200 μgHB/g were a factor of odds ratio 58.43 more at risk for CRC detection compared to women of age 56 with a FIT result of 15 μgHB/g[27]. While these differences exist, participants are still treated the same way in the population-based CRC screening programs concerning colonoscopy follow-up and oftentimes risk communication.

To compare the current FIT-only approach with the risk prediction models (Table 3) the outcome for evaluation is the area under de receiver operator curve (AUC). This area measures discrimination, that is, the ability of the test to correctly classify those with and without the disease. Since a wide variety in reporting exists in these risk prediction models (Table 3), AUC would be the most comparable and relevant statistic. 6 out of the 11 studies reported on the AUC statistic and only 3 of these compared the AUC of the FIT-only approach with their risk prediction model. These 3 studies showed a significant increase in AUC between FIT-only and their risk prediction models. The FIT-only AUCs of 0.63, 0.69 and 0.76 significantly increased to 0.69(Cooper et al., 2017), 0.76[26] and 0.84[31] respectively for these studies. Other studies, that only reported on their model's AUC reported 0.67(Auge et al., 2014), 0.67[21] and 0.7(Park et al., 2018). When comparing the AUC with the amount of included predictors in the model, it was observed that the increasing number of predictors in the model was linked to a higher AUC. For these 3 latter models and 2 other studies(van de Veerdonk et al., 2018; Chiu et al., 2016) that reported differences by other means, it can be assumed that if AUCs were reported between FIT-only and the model they would have been significantly different. This assumption is substantiated by the fact that large risk differences between participants were shown in these studies and the combination of variables that were reported, significantly predicted advanced neoplasia (Table 3). It needs to be acknowledged that all studies used advanced neoplasia (advanced adenoma and CRC) as endpoint except Li et al., (2018), who used CRC only which could explain the higher AUC(Li et al., 2018).

Regarding risk-prediction models using FIT, 2 quite different approaches appeared, namely, the '1-model approach' (based on predominantly Western studies) and the '2-step approach' (based on predominantly Asian studies) (Table 3). The 1-model approach combined all risk factors into a prediction model and assigned risk of finding advanced neoplasia to the participants. The 2-step approach disconnects the FIT from the prediction model and is used in a stepwise manner (e.g. positive FIT and risk score > 3) which is largely explained by the use of the Asia-Pacific Colorectal Screening score based-algorithm which does not include FIT. Based on the current evidence, there is no clear superior approach between the 1-model approach and the 2-step approach.

Several arguments advocate for exploring risk-stratification based on prediction models; firstly, because of the possibility to select ages < 50 for screening, considering the increasing risk for CRC in the younger population (< 50 years)(Dyer, 2018). After all, when using the current screening approach on a younger population (< 50 years) the risk of false positive FITs will increase (FIT+/Colonoscopy-). Secondly, all FIT results can be used (also the results under the FIT positivity threshold), since participants with increased CRC risk are also found in the lower FIT results (> 15 μgHB/g), as shown in Fig. 3, and even the FIT results below 15 μgHB/g[30, 54] which can lead to FIT interval CRC(van der Vlugt et al., 2017). And thirdly, this approach better discriminates between normal and neoplastic outcomes compared to the FIT-only approach as shown in this study. A theoretical, visual presentation of the possibilities with risk-stratification before colonoscopy in a population-based CRC screening program is shown in Table 2 and Fig. 4.

Fig. 4A shows FIT result distributions grouped by colonoscopy findings together with FIT positivity thresholds currently used or intended to be used. The first threshold (A1) represents 15 μgHB/g as used in the Czech Republic, Belgium and New Zealand(Schreuders et al., 2015; Ponti et al., 2017) where a large amount of people with a positive FIT undergo a negative colonoscopy(van de Veerdonk et al., 2018; Ministry of Health; New Zealand, 2018). Nevertheless, many precursor lesions will be found due to a similar FIT distribution between normal- and precursor findings (Fig. 3). The second FIT positivity threshold in Fig. 4 (A2) of 47 μgHB/g is used in the Netherlands and the last FIT positivity threshold (A3) 120 μgHB/g is intended to be used by England(Bowel Cancer UK, 2017), which will result in missing the majority of the precursor lesions and contributes to a trade-off between sensitivity for specificity as shown by prior work(Cooper et al., 2017). Altogether, there is no straightforward recommendation for a FIT positivity threshold because of the dependency on the colonoscopy resources per country, and the overlap between FIT result distributions and colonoscopy findings. A theoretical alternative could be risk-stratification as illustrated in Fig. 4B. Distributions such as Fig. 4B can be obtained when the risk-stratification before colonoscopy is superior to the FIT-only model in discriminating precursor lesions and CRC from normal results. The positivity thresholds (B1 and B2) are based on risk and seem more intuitive compared to the FIT-only approach. Using risk-stratification to decide who should undergo a colonoscopy or will be

Table 2
A theoretical comparison between the current FIT screening approach and the theoretical screening approach based on risk for 1000,000 asymptomatic CRC screening participants.

Screening approach based on FIT	Theoretical screening approach based on risk.
Target group	Model based on risk factors in asymptomatic persons
Asymptomatic persons between 50 and 74 years[b]	Gender (male or female)
	FIT (e.g. 0 to 200 μgHB/g)
	Age (e.g. 45 to 75)
	Previous non-responder (yes/no)
	Family history (yes/no)
	Location (deprived area)
	Other available validated risk factors
FIT~ > 15 μgHB/g (6.5%[a] positive or 65.000 persons)	*Based on (a hypothetical) probability threshold of ≥'X'% risk of an abnormal result.*
Colonoscopy	Colonoscopy
2.1%[a] or 21,500 negative colonoscopy (normal or non-cancerous lesions found)	1% or 10,000 negative colonoscopies (normal or non-cancerous lesions found)
2.6%[a] or 26,000 precursor lesions	3% or 30,000 precursor lesions
1.75%[a] or 17,500 carcinoma in situ or CRC	2% or 20,000 carcinoma in situ or CRC

[a] EU average based on ongoing FIT CRC screening programs (Navarro et al., 2017; Brenner and Werner, 2017; Ministry of Health; New Zealand, 2018).
[b] A commonly used population-based CRC screening target group indicator (Schreuders et al., 2015).

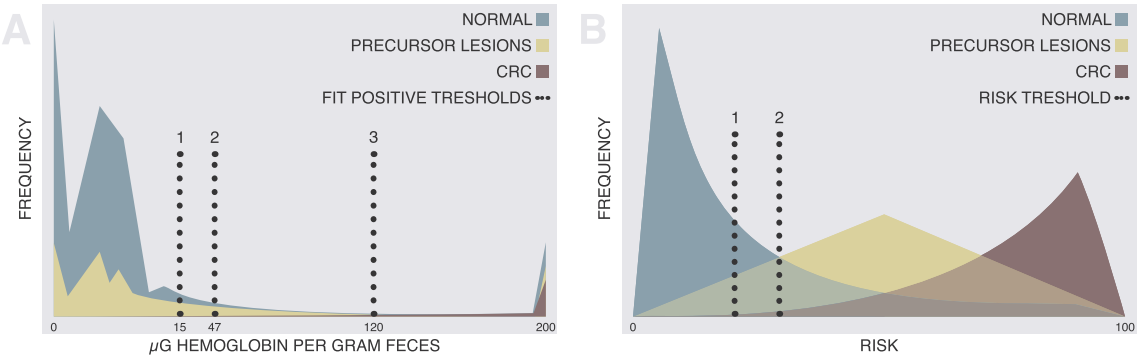

Fig. 4. Theoretical distributions based on FIT results (A) and on risk (B) including FIT and risk positivity thresholds.
Note: 4A is based on published FIT result distributions in positively screened participants(Auge et al., 2014; van de Veerdonk et al., 2018) and investigated FIT distributions below all currently used FIT positivity thresholds(Brenner and Werner, 2017).

invited for FIT in a 'X' amount of years could sound complicated in contrast to the relatively simple FIT positivity threshold. However, there is essentially no real difference in interpretation since there will always be an intuitive positivity threshold as touched upon in Fig. 4, as the FIT uses ≥'X' μgHB/g hemoglobin and risk-stratification uses ≥ 'X' probability as a threshold. Furthermore, risk-stratification in screening becomes more realistic due to high quality data combined with the emerging sophisticated prediction models as shown in recent work (Cooper et al., 2017; Urban et al., 2018).

4.1. How to proceed with risk-stratification

This study reported on multiple CRC risk factors that could be included in a prediction model combined with the FIT, and compared the discriminative power between FIT-only and the risk prediction models. Some limitations hinder risk-stratification to be used in practice(Lawler et al., 2018) as reported in the included studies (Table 3).

Ethical, legal and social issues to carry out risk-stratification and collect the necessary data before colonoscopy in a screening program are becoming increasingly important for policy-makers, healthcare professionals and stakeholders(Hall et al., 2014). The possible implications of risk-stratification before colonoscopy should be considered based on the best evidence and practical, ethical and methodological feasibility. Therefore, future studies considering models that predict CRC based on FIT and other predictors should enhance uniformity in reporting and use a structured research approach. Suggestions to reach this goal are discussed based on the evidence and limitations of the studies (Table 3).

When starting to develop a risk prediction model including FIT before colonoscopy, with the goal to better distinguish normal results from advanced neoplasia one should start with routinely available variables that are considered as CRC risk factors such as age, gender and the quantitative FIT results. Moreover, these variables are generally complete and collected in a way that is less prone to bias.

Additionally, if available, validated risk factors such as BMI, smoking and alcohol consumption can be added to the model, providing that the data collection did not cause a decrease in participation or when linkage between databases is possible, the data is reliable and complete. Adding variables to the prediction model is an important step towards the practical use of these models in pre selecting participants for colonoscopy.

Future studies should take the limitations of prior work into account because these hinder pooling, comparison and generalizability. Firstly, the goal of developing a prediction model should always be to compare the new model with the current approach, thus FIT-only vs. the prediction model using FIT. Secondly, when developing a prediction model including FIT, this should be done with a best practice standardized method. To achieve this, it is recommended to use the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) checklist(Moons et al., 2015). TRIPOD is a 22-item checklist intended to improve the reporting of prediction modelling studies in medical settings, enabling readers to better understand a prediction model study's design, conduct, analysis and interpretation, and to assess the validity, transportability and application of its results. This can only be achieved through complete transparency from authors.

Next to the TRIPOD statement, when FIT-only and risk prediction models including FIT before colonoscopy are compared, multiple statistics should be considered for reporting since these are of importance to the effectiveness of the screening program and eventually the reduction of CRC mortality(Kuipers et al., 2013). These are the participation rate of CRC, the detection rate of CRC, adenomas and non-advanced lesions, the true/false positive results and the true/false negative results so that the whole range of diagnostic statistics can be calculated. In addition, these statistics should be reported over a range of positivity thresholds of both FIT-only and the risk prediction model together with the needed colonoscopies to compare what is the optimal approach at which threshold.

5. Concluding

At this moment there is no population-based CRC screening program making use of the full potential of the quantitative FIT or combining the FIT with other available risk factors. Therefore, multiple studies advocate that including a target population purely on age and using a quantitative FIT in a qualitative manner is too crude and propose a more sophisticated use of the FIT. The FIT has much potential of uniting with other easily accessible risk factors (age, gender, quantitative FIT results) to obtain better risk predictions of detecting normal outcomes or precursor lesions and CRC before colonoscopy and without decreasing the participation or practicality of the CRC screening program. Multiple suggestions are proposed when designing such an undertaking. However, their feasibility in a population-based CRC screening program is not always entirely clear due to (mostly) practical and ethical reasons. Risk-stratification based on a prediction model including FIT for CRC creates possibilities, in the short term by risk communication and in the longer term by a tailored screening schedule of participants currently considered as average risk, shared decision making based on personal risk or individual-risk guided CRC screening. To achieve this, more high quality studies comparing FIT-only with a prediction model including FIT and other obtained CRC risk factors are necessary.

Table 3
Summary of risk-prediction models for colonoscopy taking FIT into account.

One model approach (incorporating FIT in a prediction model with multiple risk factors)

Author	Target population[g]	Study design/setting	Model(s) used	Risk factors included in model	Significant outcomes	Model limitations
Auge, J, et al. (2014)(Auge et al., 2014)	3109 FIT positive (≥20 μgHB/g) participants aged 50–69 who had a definitive outcome at colonoscopy.	Retrospective. Barcelona CRC screening program from Dec. 2009 to Feb. 2012.	Multivariable logistic regression analysis.	Age, sex and categorized FIT results (quartiles)	AUC[e] of the risk model was 0.67. Combining the risk factors, 16 risk categories were shown, with an OR[b] of 11.46 (95% CI[c], 7.25–18.10) of identifying an ACN[d] when the highest category (men, 60–69y, FIT result ≥177 μgHB/g was compared with the lowest category (women 50–59y with a FIT 20–32 μgHB/g).	No sample size calculation, internal and external validation. FIT negative results, age < 50 and age ≥ 50–75(partly) not included. Categorized age and FIT.
Stegeman et al. (2014)(Stegeman et al., 2014)	1112 participants aged 50–75 with FIT, survey and definitive colonoscopy results.	Prospective. Extracted from the COCOS RCT the Netherlands.	Multivariable logistic regression analysis.	Age, sex, BMI, smoking status, calcium intake, NSAID/aspirin, FHCRC, square root quantitative FIT result.	Discrimination significantly improved from AUC 0.69 with just FIT to 0.76 with the risk model ($P = .02$). Calibration of the risk model was good (HL[f] test; $p = .94$). Probabilities of detecting CRC were shown based on risk factors.	No sample size calculation and external validation. Age < 50 not included.
Cooper et al. (2017)(Cooper et al., 2017)	1810 FIT positive (≥20 μgHB/g) participants aged 60–75 who had a definitive outcome at colonoscopy.	Prospective. Based on the NHS BCSP FIT pilot in England from Apr. 7th to the 10th of Oct. 2014.	Neural network model and a risk-adjusted logistic regression model.	Age, sex, first time invite, previous non-responder, previous responder and quantitative FIT result.	Discrimination improved significantly from AUC 0.628 with FIT only to 0.686 with the neural network model ($P = .01$). Calibration using the HL[f] test was 0.90 for the risk-adjusted model. The sensitivity improved from 30.78% to 33.15% at similar specificity (FIT positivity threshold of 160 *μgHB/g*).	No sample size calculation and external validation. FIT negative results, < 50 years and age ≥ 50–75(partly) not included.
van de Veerdonk (2018)(van de Veerdonk et al., 2018)	57,421 FIT positive (≥15 μgHB/g) participants aged 56 to 74 with a definitive outcome at colonoscopy.	Retrospective. Population-based CRC screening program in Belgium from Oct. 2013 until July 2016.	Multivariable multinomial logistic regression analyses.	Age, sex, quantitative FIT result.	A significant difference in detecting neoplasia was found between risk profiles when combining the quantitative FIT, age and sex. The odds for detecting CRC in men aged 74, with a FIT result of ≥200 *μgHB/g*, was higher by a factor of 58.43 than that for women aged 56, with a FIT result of 15 *μgHB/g*.	No sample size calculation, internal validation, external validation and calibration. Did not include FIT negative results and < 50 years.

(*continued on next page*)

Table 3 (*continued*)

One model approach (incorporating FIT in a prediction model with multiple risk factors)

Author	Target population[g]	Study design/setting	Model(s) used	Risk factors included in model	Significant outcomes	Model limitations
Li et al. (2018)(Li et al., 2018)	550,007 FIT positive participants age 60 to 74. Not clear who of them underwent a subsequent colonoscopy.	Retrospective. Community-based CRC screening program in China in 2012.	Multivariable logistic regression analysis.	Age, sex, education level, occupations, diarrhea, constipation, colon mucosa and bleeding, gallbladder disease, a stressful life event, FHCRC and a qualitative FIT.	Discrimination of the risk model significantly increased from AUC of FIT alone 0.76 (CI: 0.74–0.79) to the AUC of the prediction model of 0.84 (CI: 0.82–0.86). The model that best predicted CRC included age, sex, education level, occupations, diarrhea, constipation, colon mucosa and bleeding, gallbladder disease, stressful life event, FH of CRC and FIT+.	No external validation. FIT negative results, age $<$ 50, age $\geq$ 50–75(partly) not included. Using a qualitative FIT

Two step approach (employing risk factors and FIT as two different preselection procedures before colonoscopy)

Author	Target populatio[g]	Study design/setting	Model(s) used	Risk factors	Significant outcomes	Model limitations
Aniwan et al. (2015)(Aniwan et al., 2015)	948 participants aged 50–75 who both participated with FIT and colonoscopy.	Cross-sectional. Hospital-based study between Feb. 2013 and July 2014 in Thailand	2 step approach. First using the APCS risk score and afterwards a FIT without using a prediction model.	Age, sex, FHCRC and smoking status as APCS risk score and a qualitative FIT.	The AUCs for CRC and ACN were 0.85 and 0.67. Non-ACR and ACN prevalence differed significantly between the 4 risk groups (P $<$ .001). Participants with both high-risk scores and FIT+ results had a significantly higher detection rate of ACN (6.15-fold,CI:[c] 3.72–10.17) compared to the other 3 groups.	No internal validation and external validation. Using FIT apart from the risk score, using a qualitative FIT and categorized age.
Chiu et al. (2016)(Chiu et al., 2016)	5657 study subjects aged 40 years and over from 15 Asia-Pacific sites.	Prospective. Multicenter study in 12 Asia-Pacific regions from Dec. 2011 to Dec. 2013.	2 step approach. APCS risk score followed by a FIT or colonoscopy without a prediction model.	Age, sex, FHCRC and smoking status as APCS[a] risk score. Low and medium risk underwent a FIT while high risk underwent a colonoscopy.	Compared with the low risk group, medium risk and high risk subjects had a 3.4-fold and a 7.8-fold increase in odds for ACN, respectively. A total of 70.6% subjects with ACN (CI: 65.6%–75.1%) and 95.1% with CRC (CI: 82.2%–99.2%) were correctly instructed to undergo a colonoscopy.	No sample size calculation, external validation and calibration. Using a qualitative FIT(partly) and FIT apart from the risk score. FIT negative results and age $<$ 50 not included. Categorized age
Knudsen et al. (2016)(Knudsen et al., 2016)	14,832 participants aged 50–74 some undergone a FIT or flexible sigmoidoscopy (FS).	Prospective. Lifestyle sub-study of the bowel Cancer screening in Norway between Nov. 2012 to sept. 2013	Multivariable logistic regression model adjusting for gender, FIT, FS and age.	A range of lifestyle factors followed by FIT or FS. Age and gender were analyzed but not specifically reported.	Adherence to multiple health recommendations was associated with decreased risk of detecting ACN. Regarding single health recommendations, non-smoking and moderate alcohol intake were lifestyle factors associated with low risk of ACN by OR(CI) 0.53 (0.42–0.68) and 0.63 (0.43–0.93).	No sample size calculation, external validation and calibration. Using FIT apart from the risk score. Unknown if FIT is qualitative or quantitative.

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Table 3 (*continued*)

Two step approach (employing risk factors and FIT as two different preselection procedures before colonoscopy)

Author	Target populatio[g]	Study design/setting	Model(s) used	Risk factors	Significant outcomes	Model limitations
Jung et al. (2018)(Jung et al., 2018a)	12,420 participants aged 40 and over, some undergone a FIT or colonoscopy and had a definitive outcome at colonoscopy.	Retrospective. Subset of the Korean Kangbuk Samsung health study from 2010 to 2014.	2 step approach. First using the APCS risk score and afterwards a FIT or colonoscopy without using a prediction model.	Age, sex, FHCRC and smoking status as APCS[a] risk score. 40-49y participants with APCS[a] ≥ 2 underwent a categorized FIT while APCS < 2 were observed.	The prevalence of ACN in participants aged 40–49 was 1.0%, 2.1%, 7.1%, and 13.4% in the FIT- & APCS < 2, FIT- & APCS ≥ 2, FIT+ & APCS < 2, and FIT+ & APCS ≥ 2 groups, respectively. The prevalence of ACN in FIT+ & APCS ≥ 2 group was higher than in participants ≥ 50 years old with APCS ≥ 4 (13.4% vs. 5.8%, $P < .001$).	No sample size calculation, internal validation, external validation and calibration. Using FIT apart from the risk score.
Jung et al. (2018)(Jung et al., 2018b)	12,270 participants age 40 and over, some undergone a FIT or colonoscopy and had a definitive outcome at colonoscopy.	Retrospective. Subset of the Korean Kangbuk Samsung health study from 2010 to 2014.	Multivariable logistic regression model stratified for FIT positive and FIT negative participants.	Point scores based on age, sex, smoking habits, BMI, NSAID use, FHCRC, hypertension (only in negative FIT), history of CVA (only in negative FIT). Followed up by categorized FIT.	Proportions of ACN[d] in FIT- persons increased as risk scores increased (from 0.6% for group 0–4 points to 8.1% for group 35–39 points), which was significantly lower compared to FIT+ persons (14.9%). Still, no statistical difference between the proportion of ACN in FIT- persons (≥40 points) and FIT+ persons was reached (10.5% vs. 14.9%, $P = .321$).	No sample size calculation, internal validation and external validation. Using FIT apart from the prediction model, categorized age.
Park et al. (2018)(Park et al., 2018)	34,658 participants of 30 years and older who undergone both FIT and colonoscopy	Retrospective. Subset of the Korean Kangbuk Samsung health study from 2004 to 2015.	Multivariable logistic regression model.	Age, sex, smoking habits, BMI, hypertension, history of CVA, diabetes were included in the model. Followed up by categorized FIT.	The discriminative power of the model was 0.700 (95% CI = 0.679–0.722).The R^2 of the logistic regression model was 5.65%. The model showed good calibration with the goodness-of-fit test ($P = .350$).	No sample size calculation and external validation. Using FIT apart from the prediction model. Age ≥ 66 was categorized.

[a] Asia-Pacific Colorectal Screening.
[b] Odds ratio.
[c] Confidence interval.
[d] Advanced colorectal neoplasia.
[e] Area under the Receiver Operating Characteristic curve.
[f] Hosmer–Lemeshow test.
[g] All participants were asymptomatic for CRC.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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