Learning to be More Positive About FIT

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Abstract: Systematic application of the fecal immunochemical test (FIT) as a screen for colorectal cancer has been shown to meaningfully impact colorectal cancer incidence and mortality. However, there is room for improvement. FIT performance is impacted by a host of patient level factors such as sex and medication use. Meta-analysis has defined those factors most likely to result in a false positive or false negative test. Further work determining how best to gather information on important factors and incorporate them into the FIT result will further enhance the accuracy and outcomes accomplished with this valuable screening test.

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An advantage of colorectal cancer (CRC) screening with the fecal immunochemical test (FIT) is the simplicity of its application. Screening can be accomplished at home with a single stool sample. In organized health care settings (e.g., health maintenance organizations or the Department of Veterans Affairs) and using electronic medical record data about screening status, the test could be mailed to those who are currently due for screening without a in office evaluation. At a basic level, interpretation is also quite straightforward. The test is resulted as "positive" or "negative". Those with a positive test, indicative of blood in the stool, are referred for colonoscopy and those with a negative test are encouraged to be rescreened at a defined interval (i.e., annually in the US).

This simplistic view of FIT serves as a valuable construct for those charged with explaining the "nuts and bolts" of the test during a busy office visit. Of course, like most diagnostic tests, there is significantly more complexity here. There are numerous FIT brands that vary both in the hemoglobin threshold used to define a positive test [1] and reliability of performance [2]. There are factors, such as ambient temperature and transportation time to the lab that can influence test results [3, 4]. There are also patient factors that might influence the accuracy of FIT .

In this month's journal, de Klerk and colleagues closely examine the impact of patient characteristics on FIT performance [5]. The starting point for their work (along with some of their key findings) is depicted in Fig. 1. When FIT is resulted as either positive or negative, one of two outcomes has occurred. The test may have worked, putting the individual in the appropriate bin of having disease (e.g., colorectal cancer or advanced neoplasia) or not. The alternative is that the test failed to correctly classify disease status. It is this latter circumstance that is the focus of the paper. Namely, the paper describes patient factors that reliably predict a greater frequency of false positive or false negative results.

The authors performed a meta-analysis of the literature to examine this question. After a careful culling of relevant papers, they identified 14 informative studies. With regards to FIT false positivity, key findings included the observation that those taking NSAID's (relative to those not exposed) were at higher risk (RR 1.16; 95% CI 1.06, 1.27). However, there was not a higher risk of false positivity for those taking anticoagulants or antithrombotics (relative to those not exposed to those drugs) with a relative risk that approached unity (RR 1.01; 95% CI 0.96, 1.06). Key factors associated with false negative results included male sex (RR 1.83; 95% CI 1.53, 2.19), family history of CRC (RR 1.61; 95% CI 1.19, 2.15), and smoking (RR 1.93; 95% CI 1.52, 2.45).

With respect to immediate clinical impact, the most important finding of the work pertains to the lack of an association between anticoagulant and antithrombotic use and false positivity. Unarguably, adherence is a critical factor driving the success of any screening program [6]. Complicating FIT application by requiring modification of an individual's daily medications regime undoubtedly would negatively impact adherence. The results of this meta-analysis are powerful evidence that such modification is not necessary and provide further weight to recommendations by organizations not to adjust intake of these compounds when screening with FIT [7]. The authors did find some small increase in risk for false positivity with NSAID intake. However, this result was based on only two studies and only one showed a significant effect. Given the importance of adherence, modifying intake of these commonly used compounds would not appear warranted.

While the examination of false positivity is of interest from a public health standpoint, most clinical endoscopists are likely little concerned about small modifications in such risk. An increase in false positivity just increases the number undergoing colonoscopy—a test that many view as the preferred strategy for screening. From this perspective, of greater concern are factors that increase the likelihood of a false negative test.

Of all the factors examined, the most important result to consider is sex. The magnitude of the effect of this variable relative to the others examined was one of the largest (i.e., an 83% increase in false negative results for men relative to women). Moreover, results

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FIT result	Colonoscopy result for advanced neoplasia (gold standard)	
	Positive	*Negative*
Positive	True positive	NSAID use
Negative	Male sex Family history Smoking	True negative

Fig. 1 Summary of factors associated with false positive and false negative FIT

for this factor were based on the largest number of studies ($n = 4$) and in the methodologically strongest studies [8, 9] the effect was the most robust. Finally, unlike many of the other factors that might be somewhat difficult to assess without formal evaluation or survey (e.g., BMI, smoking), this variable is widely available and easily accessed in any health care system or setting.

So, why might FIT perform differently in men and women? While there are a number of potential explanations, the most important factor driving higher false negative rates in men than women likely has to do with the prevalence of colonic neoplasia by sex in any given age strata [10, 11]. Given that men (at any given age) are more likely to have some type of neoplasia than women [10, 11], statistically, the test is just more likely to miss it.

So, from a clinical standpoint, what is the path forward here with regards to tailoring FIT application by sex? At the current time, there are two choices. One alternative is developing a more complicated approach to FIT-based screening programs. For example, the hemoglobin threshold for defining a positive test could be lowered in men relative to women, thus improving its sensitivity. However, this would also negatively impact the specificity creating even more false positive tests in men. It would also likely only be practical if a quantitative FIT (like OC Sensor® or FOB Gold®) were used. However, this might be particularly problematic in the United States. While the OC Sensor® is a quantitative test, it is applied qualitatively, using the FDA cleared cut-off of 20 μg hemoglobin/gm stool. So, while applying a different quantitative threshold by sex is technically possible for the laboratory, most programs would likely not want to deal with this complexity (e.g., running samples separately by sex; adjusting the cut point between runs) and using the test in a way that it was not cleared by FDA. Another approach to improving FIT accuracy within program would be staggering the starting age between the two sexes. While this would have less of an effect on improving sensitivity in the male population, delaying the female starting age for FIT could improve specificity in that group.

Likely, the better path forward for the time being would be to ignore this difference in test performance by sex and continue to apply the test equally without modification. From a public health standpoint, this leaves in place a relatively clean public health message that men and women should be screened equally. This straightforward approach may, in fact, increase adherence. For example, there is some limited evidence that spouses are more likely to be screened together [12]. So, keeping it simple is likely the preferred approach for now.

However, the work by de Klerk and colleagues puts in focus how personal factors do directly impact FIT performance. The purpose of FIT is to get the right folks to colonoscopy and undoubtedly the test could be improved by incorporating knowledge about personal risk factors. In one study, the use of a risk based prediction model incorporating both the quantitative FIT value and risk factor information (e.g., age, family history) outperformed the usual approach of classifying and individual as positive or negative based only on the FIT value (improvement in ROC curve from 0.69 to 0.76; $p = 0.02$) [13]. There are factors beyond these epidemiologic ones that might modify risk. For example, genetic factors likely are important too [14]. However, having to gather personal information and/or genetic information (e.g., from a blood draw) would significantly complicate FIT application and so future work is needed learning how to best obtain and apply this supplemental information, without compromising adherence.

The future of non-invasive screening for colorectal cancer with FIT is bright. As shown recently in the Kaiser Program, the systematic application of FIT to a population can improve adherence and meaningfully impact both CRC incidence and mortality [15]. The work by de Klerk and colleagues makes clear that there is even more we can do to make this "simple" stool test function even better. Future work determining how to efficiently and effectively gather and incorporate what we know from the patient, medical record, and stool hemoglobin value will only improve on the impressive patient related outcomes that are already being obtained with FIT.

CONFLICT OF INTEREST

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