

Guaiac based faecal occult blood testing for colorectal cancer screening: an obsolete strategy?

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The recent paper by Scholefield and colleagues¹ on the 20 year follow-up of the 'Nottingham' randomised controlled trial of guaiac based faecal occult blood test (gFOBT) colorectal cancer (CRC) screening, reports an intention to screen benefit of 13% reduced mortality from CRC and a participant benefit of 18% reduction, in spite of offering only biennial screening and with only 60% first round participation (*see page 1036*). Their three 'impact' statements are an important basis for progressing screening worldwide using faecal tests.

The first impact statement is that such screening is worthwhile.

Given that several other controlled trials of gFOBT screening show mortality reduction from CRC,^{2–5} and that such screening is considered not only cost effective but cost saving,⁶ this cannot be disputed. Indeed, it is more than worthwhile—organised population based screening programmes must be implemented. However, a recent publication reviewing international programmes shows that fully organised screening is still in its infancy in many countries.⁷ Why then is CRC screening not universally accepted and/or fully implemented?

There are many reasons relating to the population, politics, public health, purse, providers of healthcare and profession. Space limitations preclude a full analysis but this recent paper by Scholefield *et al*¹

provides a platform on which to address some of these.

Their observed impact on CRC mortality of gFOBT screening was small, a reduction of just 13%, regardless of its statistical significance.¹ Furthermore, there was no significant impact on incidence despite removal of many advanced adenomas. Many now consider it possible to improve on the outcomes demonstrated in this study and would take the view that the gFOBT trials provide guidance in principle as to the value of screening but not direction on how we should proceed to implement or evolve screening programmes at this point in time.

What evidence based options do we have then to improve the effectiveness of CRC screening?

One obvious option is to increase the proportion of people who accept an invitation to be screened. Both technological and behavioural strategies can increase participation. We now know that the faecal immunochemical test for haemoglobin (FIT) simplifies the entire faecal sampling process with consequential improvement in participation rates.⁸ Behavioural strategies that increase public awareness, such as the use of an advance notification letter, also improve participation.^{9 10}

It would have been helpful if Scholefield *et al* had been able to report CRC mortality benefit relative to the number of times a participant accepted the invitation to perform the gFOBT (perhaps because of lack of power even in a study of this magnitude). We lack clear guidance on the degree to which increased frequency of participation will improve CRC mortality benefit. Interestingly, their findings show that, if screened for just one decade, the benefit lasts for at least two decades.

Another option to improve effectiveness is to use a faecal test that can detect smaller quantities of blood in the faeces and thus achieve better detection of cancer and advanced adenomas, ideally without

an unacceptable reduction in specificity. This can clearly be achieved using FIT. FIT is better than gFOBT at detecting cancer and substantially better at detecting adenomas.^{11 12} Moreover, FIT provides quantitative faecal haemoglobin measurements that enables the user to choose the faecal haemoglobin cut-off concentration that determines who proceeds to diagnostic verification; this in turn enables control of the colonoscopy workload.¹³ In the medium sized population controlled Dutch trial which compared gFOBT with FIT,¹⁴ FIT detected twice as many people with advanced neoplasia (ie, cancer or 'advanced' adenomas) than gFOBT. While the colonoscopic effort was twice that used for gFOBT, the marked increase in lesion detection seems worth the effort.

Scholefield *et al* report that, in the invited group, an extra 615 'advanced' adenomas were identified as being removed following a positive gFOBT.¹ Since their study had 90% power to detect a 10% difference in incidence between groups, and since each group had about 2200 cancers, then a strategy that reduced incidence of cancer by about 220 might have proved significant. Putting it another way, removing 615 advanced adenomas failed to prevent 220 cancers in the time frame of observation. That this effect was not observed led Scholefield *et al* to speculate that adenoma dwell time might be longer than 10–15 years. Alternatively, or in addition, it might be that less than one-third of advanced adenomas are destined to progress to cancer. Whatever the case and despite these crude calculations, if an impact on incidence within two decades is to be attained, detection and removal of more adenomas than was achieved in this trial seems mandatory. This is supported by the comments by Scholefield *et al* on the Minnesota trial where a reduction in CRC incidence was observed by using a more sensitive and less specific test—rehydrated gFOBT—thus returning a much higher test positivity rate with a consequently greater rate of adenoma removal.²

CRC screening using faecal tests has the capacity to prevent cancer by detection and removal of adenomas if the test used is sufficiently sensitive.¹⁵ Whether the extra effort needed to improve adenoma detection and removal is feasible, affordable or considered cost effective remains an issue for debate but the results reported by Scholefield *et al* indicate that a low sensitivity gFOBT will not reduce incidence. How many adenomas really do need to be removed to prevent one cancer is the unanswered question.

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Their second impact statement is that the 'National Bowel Cancer Screening Programme' would be expected to deliver a CRC mortality reduction (it should be noted that four countries are screening in the UK and their approaches differ). While such an impact is very likely, it seems accepting of a small benefit when a greater benefit is achievable. With FIT, we now have faecal screening tests that are more acceptable to participants and possess markedly better analytical and clinical performance characteristics. When used at conventional cut-off concentrations, FIT usually requires more follow-up colonoscopies but the effort is not disproportionate to the improvements in lesion detection.¹⁴ Furthermore, the use of a quantitative FIT enables objective choice of the desirable clinical performance characteristics, something gFOBT cannot deliver. The challenge for a CRC screening programme is to develop a high quality colonoscopy resource so that the many operational, analytical and clinical advantages of FIT can be effectively exploited.

In short, current evidence makes it clear that using gFOBT for screening is a choice for a less effective test. This is why the European Guidelines for CRC Screening now recommend the use of FIT.¹⁶

Scholefield *et al* implied support for this conclusion in their third impact statement which states that the door is open to new screening methodologies, specifically 'immunological (*sic*) FOBT'. In 1993–1996, the initial publications of the randomised controlled trials of gFOBT screening proved population benefit^{2 3 17}; two decades later we have a proven, improved screening test—FIT! gFOBT has successfully underpinned many efforts in

screening but FIT provides enhanced analytical, logistical and clinical attributes that allow successful management of workloads and optimisation of clinical performance. Whether gFOBT passes into history in CRC screening is now in the hands of those who organise large scale programmes.

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