Personalised screening for colorectal cancer, ready for take-off

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Colorectal cancer (CRC) is among the most common causes of cancer-related mortality.[1] For the purpose of population-based CRC screening, faecal immunochemical tests (FIT) have been widely accepted.[2] FIT can both be used in a qualitative manner, leading to either a positive or negative result, or a quantitative manner resulting in the reporting of microgram faecal haemoglobin (Hb) per gram faeces. Screenees with a FIT result above a prespecified threshold are referred for colonoscopy. A higher faecal Hb concentration is associated with a higher risk of advanced neoplasia.[3 4] Most screening programmes use quantitative FIT. The results are however habitually reported in a dichotomised manner (ie, below or above a prespecified threshold). Such a dichotomised strategy subsequently misses out on countless possibilities in which the exact faecal Hb concentration could guide clinical decision-making. One of these possibilities is the use of negative FIT results, in other words faecal Hb concentrations below the accepted cut-off, as a predictor for the risk of advanced neoplasia in following screening rounds.

The beautiful paper by Senore and colleagues in *Gut* provides additional support for this concept in exploring the predictive value of faecal Hb concentrations over multiple rounds of CRC screening.[5] Their study used data from four Italian CRC screening programme over multiple rounds including almost 300 000 screenees. Screenees with a faecal Hb concentration below the cut-off of 20 µg Hb/g faeces were included for analysis. These individuals were followed up for a maximum of four rounds. Both screen-detected CRCs as well as interval CRCs were reported. The results confirmed the association of cumulative faecal Hb concentrations with subsequent advanced neoplasia and CRC. The risk of being diagnosed with CRC during follow-up progressively increased with higher Hb concentrations up to 39-fold for those with a faecal Hb concentration just below the threshold (19.9 µg Hb/g faeces) compared with screenees with non-detectable faecal Hb. In line with these findings, the risk of interval CRC was increased in those with high cumulative faecal Hb concentrations leading to a 24-fold increase in incidence rate.

Senore and his colleagues are not the first to explore faecal Hb concentrations of negative FITs. A Taiwanese study, using the same cut-off as in the Italian programmes, already showed that a below threshold faecal Hb concentration could act as predictor of incident advanced neoplasia at follow-up.[6] This study was however criticised for its peculiar design of once-only FIT with fairly high cut-off. It basically confirmed other single-round data that had shown that subjects with a faecal Hb concentration between 10 and 20 µg/g faeces have an up to 40% risk of advanced neoplasia either found at baseline when doing immediate colonoscopy, or during follow-up as symptomatic lesion when adopting a wait and see policy.[4] In line with these results, a recent Spanish study reported an OR for advanced neoplasia of nearly 22 for those with high faecal Hb concentrations (between 10 and 19.9 µg/g faeces) compared with those with low Hb concentrations (between 0 and 3.8 µg/g faeces).[7] Both studies reported risks that were lower than those reported by Senore et al.[5] This could be explained by the fact that the Italian findings were set against screenees with undetectable faecal Hb concentrations whereas the other studies compared their findings to those with low, yet not undetectable concentrations. The results of this Italian study are also in line with the results from a Dutch CRC screening cohort.[8] Though the threshold used in this study was much lower (10 µg/g faeces), screenees with a faecal Hb concentration just under the threshold had an eightfold increase of long-term risk of advanced neoplasia over four screening rounds.[8] These results were based on a smaller cohort limiting additional subgroup analyses on interval cancers and CRC location. Senore *et al* did report on the relationship between the location of CRC and faecal Hb concentration, indicating that among those testing positive at the third round the proportion of proximal CRC tended to be higher compared with those testing positive at the second round.

The Italian data published in *Gut* combined with the two previous similar studies from Spain and the Netherlands now firmly establish ground for development of personalised FIT screening strategies using individual actual faecal Hb data.[5 7 8] These findings have the potential to help move risk stratification along and to aid public health decision makers in choosing the optimal screening strategy in FIT-based CRC screening. This can be done in any programme irrespective of the a priori selected cut-off and screening interval. It would imply the concept that the FIT screening interval and the decision to refer to colonoscopy would depend on the actual faecal Hb concentration and its changes over time in consecutive screening rounds. Screenees who repeatedly have undetectable or very low faecal Hb levels could then be tested at larger than average intervals, whereas subjects who reach a cumulative cut-off over different rounds are considered for more frequent testing or direct colonoscopy referral. Such an approach would mimic algorithms used in prostate cancer screening based on the actual level and change over time of prostate specific antigen concentration. Such a strategy can improve cancer detection while reducing the need for prostate biopsies.[9] In line with such a strategy, the predictive ability of quantitative FIT results paves the way for using FIT-based algorithms for personalised CRC screening. We may expect to soon see the first pilots adapting such an approach. It has the potential to bring FIT screening to the next level, improving early detection of progressive lesions, while reducing burden for those at low risk.

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