The impact of a comprehensive risk prediction model for colorectal cancer on a population screening program

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ABSTRACT

Background: In many countries, population colorectal cancer (CRC) screening is based on age and family history, though more precise risk prediction could better target screening. We examined the impact of a CRC risk prediction model (incorporating age, sex, lifestyle, genomic and family history factors) to target screening under several feasible screening scenarios.

Methods: We estimated the model’s predicted CRC risk distribution in the Australian population. Predicted CRC risks were categorised into screening recommendations under three proposed scenarios to compare to current recommendations: a) highly tailored; b) three risk categories; c) four sex-specific risk categories. Under each scenario, for 35-74-year-olds, we calculated the number of CRC screens by immunochemical faecal occult blood testing (iFOBT) and colonoscopy, and the proportion of predicted CRCs over ten years in each screening group.

Results: Currently, 1.1% of 35-74-year-olds are recommended screening colonoscopy and 56.2% iFOBT. 5.7% and 83.2% of CRCs over ten years were predicted to occur in these groups respectively. For the scenarios: a) colonoscopy was recommended to 8.1% and iFOBT to 37.5%, with 36.1% and 50.1% of CRCs in each group; b) colonoscopy recommended to 2.4% and iFOBT to 56.0%, with 13.2% and 76.9% of cancers in each group; c) colonoscopy recommended to 5.0% and iFOBT to 54.2%, with 24.5% and 66.5% of cancers in each group.

Conclusions: A highly tailored CRC screening scenario results in many fewer screens but more cancers in those unscreened. Category-based scenarios may provide good balance between number of screens and cancers detected and be simpler to implement.

Keywords: cancer screening; risk prediction; colorectal cancer; polygenic risk score; clinical utility
Most countries with guidelines for colorectal cancer (CRC) screening recommend faecal occult blood testing (FOBT), with diagnostic colonoscopy for positive tests, to all within an age range (usually 50 and 75 years)(1). More intensive screening is recommended for those with higher risks due to their family history of CRC, usually screening colonoscopy instead of FOBT(2,3). Colonoscopy is more sensitive and specific but carries greater cost and risk, therefore reserved for higher risk individuals. The recommended starting age and frequency of colonoscopy varies between countries but generally, intensity increases with strength of family history. Australian guidelines have three broad screening categories that incorporate family history: none or minimal; moderate; or strong family history (Figure 1)(4,5). Most people with CRC do not have a family history, so alone it is not a frequent predictor of disease risk.

Additional, more common factors influencing future CRC risk provide potential for risk-based screening. These include lifestyle exposures, personal characteristics, rare high-risk genetic variants, and common genomic factors(6-13). Many CRC risk prediction models have been developed including combinations of these factors; given these exposures’ high prevalence, risk prediction utilising them is potentially applicable to much more of the population than family history. If these models could be administered to large proportions of a population to estimate personal risk, tailored cancer screening would be possible. This could be more cost-effective than the current model using only family history, since screening could be targeted more efficiently and the burden of false positive FOBT screens or unnecessary screens to those at low risk could be reduced.

Many risk prediction models have been evaluated for their ability to differentiate those who will develop CRC from those who do not, using discrimination measures such as area under the receiver operating characteristic curve (AUROC)(6,14-16). AUROC has limited clinical relevance and does not reflect a model’s ability to stratify risk within the population(17-20). A better indicator of clinical utility is the model’s ability to identify a small proportion of the population where a large proportion of risk lies. No studies have explicitly explored how existing risk models for CRC stratify risk within the general population.
Other analyses have modelled the impact of genomic and lifestyle models on CRC screening programs, proposing scenarios where each person begins screening when their individual risk of CRC, based on personal risk factors, reaches a pre-defined threshold(15,16,21-26). These scenarios require substantial tailoring, given individuals could potentially begin screening over a wide range of ages, some earlier and some later than the current system. This very tailored program may present not only implementation challenges, but de-implementation challenges; recent studies have shown limited acceptability of beginning screening at a later age, despite a known lower risk of cancer(27,28).

Additionally, while electronic medical records are increasing in frequency and efficiency, continuous documentation of specific risk information from the time of risk assessment to the commencement of screening may prove difficult with infrastructure upgrades and patient mobility(29). It is possible that simpler screening algorithms that are similar to the current category-based system but incorporate more precise risk prediction may be more practical to implement.

No studies have examined whether a simpler, categorical risk-based model, and one where the latest age for commencing screening is the same as the current system, would result in similar screening efficiency gains to the very tailored programs proposed previously. We explored the impact of a lifestyle and genomic risk prediction model for CRC on screening in the Australian population, proposing more feasible screening algorithms, and assessing their impact on the number of people who would be screened and the number of cancers that would occur in those screened groups. This analysis also provides a framework into which newer risk prediction models can be inserted as they become more predictive and accurate, and provides a basis for the future work that should take place to address the implementation challenges of a risk-stratified CRC screening program.
METHODS

Study Design

We estimated the distribution of a comprehensive risk model’s predicted risks in the Australian population (based on family history, lifestyle and genomic risk factors). We then calculated the number of people and CRC cases recommended to have no screening, immunochemical (iFOBT) screening, and colonoscopic screening under different screening scenarios that are based (in different ways) on predicted risk from the model.

Risk Prediction Models and Distributions

We calculated the distribution of predicted lifestyle risk using self-reported values for ten factors from the CRISP model(30) for 4 747 control participants from the Australasian Colorectal Cancer Family Registry (ACCFR)(31) who reported family history of CRC (Supplementary Methods/Supplementary Table 1). Each person’s risk due to family history was based on number, degree of relatedness and age at diagnosis of relatives with CRC (Supplementary Methods). Each person’s genomic risk was simulated using the theoretical relative risk distribution in the Caucasian population from 45 CRC-associated single nucleotide polymorphisms (SNPs) (Supplementary Methods/Supplementary Table 2)(24).

To determine the number of people and cases in each screening category, we implemented a mixture of non-parametric and parametric bootstrapping, drawing 500 samples. Each sample of 4 000 people was drawn with replacement from the 4 747 ACCFR participants (each having lifestyle and family history risks) then genomic risks were simulated for each, sampling from the genomic risk distribution. As there is currently no evidence of interactive effects between the three types of risk (family history is only weakly associated with these SNPs)(15,32), lifestyle, genomic, and family history relative risks were combined on a log-additive scale. In a supplementary analysis, we examined the genomic and lifestyle models separately (each with family history). Relative risks for CRC were converted to absolute risks using Australian incidences for CRC(33) (Supplementary Methods).
For each bootstrap sample, under each described screening scenario, we calculated the proportion of Australians aged 35-74 recommended to have no screening, iFOBT screening, or colonoscopic screening. The age limits of 35-74 were chosen to reflect the earliest and latest ages at which a person may be recommended CRC screening under the current Australian guidelines(5). The proportion of cases expected in each screening category was calculated from absolute risks, with our final estimates being the medians over all bootstrapped samples and 95% CIs being the 2.5th and 97.5th percentiles. Proportions were converted to absolute numbers using the projected Australian population figures for 2020(34). All analyses were completed in R(35).

**Customising Screening Based on Risk**

We created several implementation scenarios for how CRC risk could be converted to screening recommendations. Scenarios were deliberately designed to reflect previously simulated scenarios(15,21,23) and pragmatic scenarios within limitations of current population screening programs. This resulted in three proposals to compare to scenario 1 (Figure 1).

Scenario 1: Current Australian screening guidelines use family history to classify individuals into three risk categories(4,5), developed to incorporate approximate relative risks conferred by constellations of family history (Category 1: relative risk (RR) ≤2; Category 2: 2<RR≤6; Category 3: RR>6).

Scenario 2: A highly tailored approach: screening is based on absolute risk exceeding two thresholds. iFOBT, then colonoscopy, would begin when one’s 10-year-risk of CRC exceeds 0.9% (equalling the average 10-year-risk of CRC for an Australian aged 50 years, the current starting age for screening)(33) and 4.0% (in current Australian guidelines this threshold balances cancer risk with risk of complications from colonoscopy)(36) respectively. In two sensitivity analyses, these absolute risk thresholds were altered to match the total number of screeners (scenarios 2a) or cases (scenario 2b) as the current guidelines (Supplementary Methods).

Scenario 3: Screening is based on three risk categories; the ages where screening is offered mirrors scenario 1 but screening category is determined by a relative risk threshold calculated using
the risk prediction model (Figure 1). The relative risk thresholds were chosen to reflect those used in the current Australian guidelines (Category 1: RR≤2; Category 2: 2<RR≤6; Category 3: RR>6).

Scenario 4: Screening is similar to scenario 3, with more precision added as an additional screening category and varying relative risk thresholds for men and women to reflect differing incidence rates by sex (men: Category 1: RR≤1.5; Category 1a: 1.5<RR≤2.5; Category 2: 2.5<RR≤5; Category 3: RR>5; women: Category 1: RR≤2; Category 1a: 2<RR≤3.5; Category 2: 3.5<RR≤7; Category 3: RR>7).

RESULTS

Summary

The proportions and absolute numbers of the Australian population aged 35-74 who would be recommended screening for CRC via iFOBT and colonoscopy under each scenario, and the respective proportions of CRCs expected in the next ten years in each of these three groups, are seen in Figure 2 (comprehensive model), and Supplementary Figure 1 (genomic and lifestyle model separately).

Scenario 1 – Current Guidelines

Figure 2A shows that 5.7% of CRCs in the next ten years (10 239 cancers) are expected to occur in 1.1% of 35-74-year-olds in Australia (130 928 people) whose age and family history warrant colonoscopy every five years; 83.2% of CRCs in the next ten years (149 264 cancers) are expected to occur in the 56.2% of 35-74-year-olds (6 870 462 people) recommended biennial iFOBT screening; and 11.1% of CRCs in the next ten years (19 856 cancers) are expected in the 42.7% (5 219 735 people) not recommended screening.

Scenarios using Risk Prediction Models

Scenario 2 (Figure 2B) adds the risk prediction model. Compared with scenario 1, approximately 8 times more people (~850 000) would be recommended colonoscopy, and approximately 1.4 million more people would not be recommended screening. This tailored scenario
would result in a substantial rise in the expected proportion of future CRCs that would occur in the 8.1% recommended the more sensitive colonoscopic screening (36.1% of cancers in next ten years, 64 762 cases) but also an increase in the proportion occurring in those not screened (13.8%, 24 699 cases, would occur in the 54.5% not screened). The remaining 37.5% would be recommended screening with iFOBT and 50.1% of future CRCs would occur in that group.

Supplementary Table 3 shows that despite screening the same number of people as in scenario 1, under scenario 2a, more cancers were expected to occur in those recommended colonoscopy compared with scenario 1 (8.0% vs 5.7% of cancers over the next ten years, translating to 14 296 vs 10 239 cases) and fewer expected cancers in those not being screened (9.0% vs 11.1%, translating to 16 069 vs 19 856 cases). Under scenario 2b, approximately half as many people needed to be screened to detect the same number of cancers in the colonoscopy group (70 163 vs 130 928) and fewer in the iFOBT group (6 281 328 vs 6 870 462) compared with scenario 1.

Figure 2C-D shows scenarios 3 and 4. Under the two scenarios based on broader risk categories, the proportion of the population recommended colonoscopy screening (scenario 3: 2.4%; scenario 4: 5.0%) was less than for scenario 2 but more than for scenario 1. Slightly fewer people would be recommended to have iFOBT screening compared with scenario 1 (scenario 3: 56.0%; scenario 4: 54.2%; scenario 1: 56.2%) and fewer cancers would occur in this group (scenario 3: 76.9%; scenario 4: 66.5%; scenario 1: 83.2%). However, slightly fewer cancers would also occur in the non-screened group for both scenarios 3 and 4 compared to scenario 1 (scenario 3: 9.9%; scenario 4: 9.1%; scenario 1: 11.1%). Therefore more cancers would be expected to occur in the highest risk colonoscopy group (scenario 3: 13.2%; scenario 4: 24.5%; scenario 1: 5.7%).

**DISCUSSION**

This study shows the potential impact on a population screening program of two CRC risk prediction models when implemented under different screening scenarios. We show that adding lifestyle and genomic risk to family history and age using simple screening algorithms, would identify
a larger number of people for screening who are expected to develop CRC. The balance of complexity of the risk stratification process and screening algorithm, number of screens performed, and number of cancers detected warrants consideration. Though this study focusses on impact in the Australian context, these principles can be applied to other populations, particularly countries with population CRC screening programs, reserving the more invasive colonoscopy for those at increased risk due to family history.

A substantial strength of our analysis is that we have incorporated not only the distribution of each individual risk factor (for example, the proportion of the population who eat red meat more than once per day) but also the complex interdependencies between these risk factors, including family history of CRC (for example, the proportion of the population who eat red meat more than once per day and take aspirin and have a family history of CRC). This is unlike other studies that have modelled population CRC risks based on lifestyle exposures(22).

Previous analyses of cancer risk prediction models’ clinical utility have considered scenario 2, where screening would be offered to individuals upon reaching an absolute risk threshold(17,21,37). Change from current practice, where most receive the same screening at the same age, to this personalised model, could present implementation and de-implementation barriers(29). A lesser shift, potentially more implementable, comprises personalised models that use risk categories (scenarios 3 and 4), not hitherto assessed. We quantify some of the “trade-offs” of a simpler, categorical scenario instead of a highly personalised one.

We demonstrated that a personally tailored model (scenario 2) would substantially reduce the number of total screens (~1.4 million fewer, 22% decrease) but increase the number of cancers expected to occur in those unscreened (~5 000 more cancers over 10 years, a 24% increase). A similar analysis suggested this limitation of risk models to guide cancer screening(21), with reduced screening for those with a low, but non-zero, risk. This is not surprising, considering the distribution of cancer risk within the population(38). While everyone in the sizable portion of the population at the bottom of the distribution has a low risk, which warrants delaying screening to an older age, the sheer volume of people in this category means additional cancers will go unscreened. Following research
showing that 85% of women would increase breast screening based on a higher personal genomic risk, but fewer (59%) would decrease their screening if found to be low risk (27), this approach may not be acceptable to the general population.

With scenarios 2a and 2b, we directly evaluated the value added by the risk prediction model. These scenarios were like scenario 2 but absolute risk thresholds set to compare directly to the baseline scenario. Scenario 2a shows that with current screening numbers, a greater proportion of cancers will occur in those screening. Scenario 2b shows that to detect the same number of cancers currently found, fewer people need be screened. This highlights the superiority of the risk prediction model compared to only age and family history, and the sensitivity of the impact of a cancer screening program to risk threshold cut-offs, underlining the importance of modelling screening scenarios.

A better scenario may retain broad risk categories for screening, determining screening category using more accurate risk prediction models than family history alone (scenarios 3/4). Everyone aged over 50 would be recommended some screening, in line with current guidelines, potentially decreasing de-implementation challenges of reduction of screening. While scenarios 3 and 4 resulted in slightly more screening overall (as would any scenario that aims to avoid de-implementation issues), there were more cancers detected in those screened, particularly those with colonoscopy.

This analysis also allowed direct comparison of the lifestyle model, genomic model, and combined risk prediction model. While the combined risk prediction model always resulted in more cancers occurring in screened groups than each model alone, its implementation is likely to be more laborious, requiring both genomic analysis and collection of lifestyle risk factors. Neither the genomic nor the lifestyle model alone surpassed the other (numbers of cancers predicted to be detected by screening); other logistical aspects of implementing each model warrant consideration if choosing to implement only one. There have already been several studies examining the feasibility of administering personalised cancer risk information to the general public within primary care/family practice (39-41) and within centralised cancer screening programs (42), suggesting they may be feasible. Nonetheless, additional implementation research is required to understand how risk stratified
screening, using genomic and/or lifestyle models, can be embedded in routine care. Other analyses in colorectal(22) and breast cancer(43) demonstrated that the potential for the greatest risk reductions is in those at the highest genomic risk; a combined risk model, with targeted behavioural and screening interventions to those with highest genomic risk, may be optimal.

This study is modelled and therefore based on expected numbers of future cases. This relies on the important assumption that the risk prediction models are well calibrated. This assumption has been found true for the CRISP model in the Australian population(44), but, to the best of our knowledge, not for genomic CRC risk prediction models. Calibration is less studied(15,16,18,20), but several genomic breast cancer risk prediction models are well calibrated(45,46) The methods to develop these are comparable to our genomic model, inferring that our model could show a similar level of calibration. Each of the lifestyle and genomic models has been separately internally and externally validated but not the combined model. Despite these limitations, we provide practical findings for potential clinical impact of this model. Calibration studies of genomic models, and validation studies of comprehensive models should be a priority in the future.

The CRISP and genomic models, like many risk prediction models, have been developed primarily from data collected from those of Caucasian ethnicity(6,47). There are important efforts to redress this imbalance in new studies, particularly in the development of genomic tests(48,49). When these more generalisable models are developed, they could be incorporated into future analyses using similar methods to ours.

These models and scenarios in this analysis assume 100% uptake of the risk assessment and recommended screening, not consistent with current uptake(1,50). An important aspect of clinical utility is to determine the efficacy of a genomic test ‘to bring about the intended purpose … when used under the most favorable circumstances’(51), to lead into effectiveness studies examining improvement in outcomes in real-world scenarios. Future studies modelling varying uptake rates of the risk assessment, iFOBT, and colonoscopy screening tests would be useful, ideally based on data from effectiveness studies.
This analysis provides a framework into which more sophisticated risk prediction models can be incorporated. However, it also underlines that there are still noteworthy challenges to be overcome before risk-stratified screening is implementable. Risk prediction models are constantly becoming better calibrated, are more accurate in their risk prediction, their costs are reduced, and are more applicable to all ethnicities, which will go some way to ensuring a cost-effective and equitable future risk-stratified screening program.

Other questions regarding when risk assessment would take place warrant answering. One option could be a central system built within existing population screening programs to facilitate a seamless translation of risk assessment to screening recommendations. Another would see general practitioners performing the risk assessment, creating the opportunity to discuss and then manage modifiable risk factors. The latter approach may also result in greater uptake of the risk assessment and resulting screening recommendations, as demonstrated by studies involving general practitioner endorsement of iFOBT(52,53). Potential barriers to this option include upskilling the current workforce and integration into current general practitioner workflows(54). Future implementation research could determine the approach with the greatest public health impact.

Any risk-stratified screening program would likely need to be dynamic to account for improvements in the risk-prediction models, changes in incidence rates (e.g. the increasing incidence in younger adults and the impact of screening programs(55-57)), and changes in population structure. It is difficult to predict the effect of these differences on a risk-stratified program, particularly given it is still unclear what is driving the increases in incidence in young people. If these changes are due to differences in environmental exposures (which has been suggested(57)), then this will need to be reflected in all parameters in the current model. When this is elucidated, the model we present here could be updated for future analyses.

The different sensitivities of screening modalities warrant examination when modelling the potential gains from a tailored screening program. Colonoscopy, while riskier, has an ~95% sensitivity for CRC, where iFOBT is ~83% sensitive(58). The proportion of cancers which could be screen-detected according to these relative sensitivities would increase from 74.3% in scenario 1 to
77.4% in scenario 2a (the scenario where no more screens are performed). A formal cost-effectiveness analysis, considering the relative sensitivities, specificities and costs of iFOBT, colonoscopy and risk assessment consultations, are required to determine if any of these tailored screening scenarios would be cost-effective, and could incorporate the potential for genomic risk assessment to include other diseases where prediction models are available. Capacity within the health system for any additional screens required under new risk-stratified programs would also need to be considered.

This clinical utility of any risk prediction model varies, as does AUROC. As risk models improve in their precision, so will their clinical utility, but utility is also impacted by the method of implementation. This means that as models are developed, additional to traditional statistics of predictive accuracy, alternative evaluation measures are warranted with exploration of how models might be delivered to the public. This analysis provides only a starting point; an estimate of the clinical utility and potential impact of two existing risk prediction models for CRC in screening scenarios that, compared to the precise scenarios explored in previous studies, may be achievable in the real world. Future analyses using our methods could incorporate many different variables, including updated risk prediction models (which are more applicable to diverse ethnicities and better calibrated), and changes in incidence and demographics, which in turn can feed into cost-effectiveness analyses that incorporate ideal risk thresholds for screening.

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FIGURE TITLES AND LEGENDS

Figure 1: CRC screening algorithm for current Australian guidelines and two proposed scenarios: CRC screening algorithm for scenarios 1 (current Australian guidelines), scenario 3 (using relative risks determined by risk prediction models), and scenario 4 (using sex-specific relative risks determined by risk prediction models, with an additional screening category for those slightly above ‘average’ risk).

Figure 2: Proportions and number of CRC screens and predicted CRCs in each screening group in 35-74-year-old Australians: The first column (bar chart) in each panel represents the proportion (95% confidence intervals of proportions, absolute number) of 35-74-year-old Australians who would not be screened for CRC, be screened with iFOBT, and be screened with colonoscopy under each scenario. The second column (person icons) represents the proportion (95% confidence intervals of proportions, absolute number) of predicted CRCs in the next ten years that would occur in each of the screened groups. All scenarios (except scenario 1) use a combined lifestyle and genomic risk prediction model to place individuals in each screening group A) scenario 1, the current Australian guidelines; B) scenario 2, a program based on absolute risk thresholds for screening using the risk prediction model; C) scenario 3, a category-based program (3 categories not accounting for sex) using the risk prediction model; D) scenario 4, a category-based program (4 categories accounting for sex) using the risk prediction model program. Some percentages to do sum to 100% due to rounding. 95% confidence intervals for absolute numbers can be found in Supplementary Table 4.
### Figure 1

| Category | Scenario 1: Current Australian family history guidelines | Scenario 2: Relative risks | Scenario 3: Relative risks + additional category | Scenario 4: Sex-specific relative risks + additional category | Recommended Screening (Age Groups) |
|----------|--------------------------------------------------------|----------------------------|-----------------------------------------------|----------------------------------------------------------|----------------------------------|
| Both Sexes | - No family history of CRC | ≤2 | ≤1.5 | ≤2 | 35-39 | No screening | iFOBT 2-yearly |
| Both Sexes | - One FDR or SDR with CRC diagnosed ≥55 | ≤2 | ≤1.5 | ≤2 | 40-44 | No screening | iFOBT 2-yearly |
| Both Sexes | - One FDR and one SDR with CRC diagnosed ≥55 | ≤2 | ≤1.5 | ≤2 | 45-49 | No screening | iFOBT 2-yearly |
| Both Sexes | - One FDR with CRC diagnosed <55 | >2 | ≤6 | >2 | 50-59 | No screening | Coloscopy 5-yearly |
| Both Sexes | - Two FDRs with CRC diagnosed ≥55 | >2 | ≤6 | >2 | 60-74 | No screening | Coloscopy 5-yearly |
| Both Sexes | - One FDR and at least two SDRs with CRC diagnosed ≥55 | >2 | ≤6 | >2 | 60-74 | No screening | Coloscopy 5-yearly |
| Both Sexes | - At least three FDRs/SDRs with CRC; at least one diagnosed <55 | ≥6 | >5 | >7 | 60-74 | iFOBT 2-yearly | Coloscopy 5-yearly |
| Both Sexes | - At least three FDRs with CRC diagnosed ≥55 | ≥6 | >5 | >7 | 60-74 | iFOBT 2-yearly | Coloscopy 5-yearly |

Abbreviations: CRC: colorectal cancer; FDR: first-degree relative; SDR: second-degree relative
