Risk prediction analytics for the Hong Kong Colorectal Cancer Screening Programme: abridged secondary publication

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KEY MESSAGES

1. Quantitative faecal immunochemical tests (FITs) contain diverse information that can be used to explore the epidemiology of colorectal cancer (CRC).
2. Using individuals' historical FIT results, we constructed and fitted a natural history model that had moderate predictive power for advanced colorectal neoplastic diseases but suboptimal predictive power for FIT positivity.
3. Our fitted natural history model provides an evidence-based analytical platform for future evaluation and optimisation of the cost-effectiveness of CRC screening. The use of a sex-specific threshold for FIT positivity could serve as a first step to modify the current screening algorithm.
4. The screening database should be linked to screenees' electronic health records to allow access to data regarding CRC risk factors, thereby enhancing predictive model performance and facilitating evaluations of personalised screening algorithms.
5. Policymakers should monitor participation and compliance rates, with prompt support for underserved populations.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide. In the past few decades, CRC incidence and mortality have rapidly increased in Asia-Pacific countries such as China, Japan, South Korea, Australia, and Thailand. Many countries have implemented population-based CRC screening programmes.[1]

Colonoscopy is the gold standard for diagnosing colorectal neoplastic diseases. However, because of capacity constraints and potential adverse events associated with colonoscopy,[2] quantitative faecal immunochemical tests (FITs) are increasingly used to triage screenees for colonoscopy.[3] In September 2016, Hong Kong launched a 2-year FIT-based CRC screening pilot programme for residents aged 61 to 70 years. Each screenee submitted two faecal samples that had been obtained 5 days apart; screenees were referred for diagnostic colonoscopy if at least one of their two-sample FIT values (ie, FIT_2 values) was ≥100 ng/mL. In September 2018, the programme was included in routine management for individuals aged 50 to 75 years to undergo biennial FIT screening.

This study was conducted to characterise the epidemiology of colorectal neoplastic diseases and develop data analytics for the CRC screening programme in Hong Kong. The findings were used to generate epidemiologic insights, parameterise the natural history model of CRC for cost-effective analysis, and infer the presence of advanced neoplasia from FIT_2 values.

Methods

For the natural history model, we stratified screenees by disease stage based on their colonoscopy diagnosis: normal (N), hyperplastic polyps (HP), non-advanced adenoma (NA), serrated lesions (SL), advanced adenoma (AA), colorectal cancer (CRC), and unknown (U). Patients with a classification of unknown were either FIT_2-negative (both FIT_2 values <100 ng/mL) or FIT_2-positive (at least one FIT_2 value ≥100 ng/mL) but had no recorded colonoscopy diagnosis. We assumed that there were two pathways of colorectal neoplastic diseases, namely the conventional adenoma pathway ($N \rightarrow NA \rightarrow AA \rightarrow CRC \rightarrow DC$) and the serrated pathway ($N \rightarrow HP \rightarrow SL \rightarrow CRC \rightarrow DC$); *CRC* and *DC* represent preclinical (undiagnosed) and diagnosed CRC, respectively. The serrated pathway is involved in 10% to 30% of CRC cases.[4]

We developed a sex-specific model with parameters θ and fitted the model to the data by estimating θ using the Markov chain Monte Carlo method. For simplicity, we suppressed the

sex dependence of the model. Let $p(s|a,\theta)$ be the prevalence of disease stage $s\in\{N,HP,NA,SL,AA,CRC\}$ among individuals with age a who have never been diagnosed with CRC. We used the following natural history model to simulate the epidemiology of colorectal neoplastic diseases in a cohort starting at age 20 years in the absence of screening. Without loss of generality, we assumed that the initial cohort size (at age 20 years) was 1. Let $x_s(a)$ be the probability that a particular individual in the cohort had disease stage s at age a, and $\gamma_{s,s'}$ be the progression rate from disease stage s to s'. The natural history model comprised the following differential equations:

$$\frac{dx_N(a)}{da} = -(\gamma_{N,NA}(a) + \gamma_{N,HP}(a) + \mu(a))\, x_N(a)$$

$$\frac{dx_{NA}(a)}{da} = \gamma_{N,NA}\, x_N(a) - \gamma_{NA,AA} x_{NA}(a) - \mu(a) x_{NA}(a)$$

$$\frac{dx_{HP}(a)}{da} = \gamma_{N,HP}\, x_N(a) - \gamma_{HP,SL} x_{HP}(a) - \mu(a) x_{HP}(a)$$

$$\frac{dx_{AA}(a)}{da} = \gamma_{NA,AA} x_{NA}(a) - \gamma_{AA,CRC} x_{AA}(a) - \mu(a) x_{AA}(a)$$

$$\frac{dx_{SL}(a)}{da} = \gamma_{HP,SL} x_{HP}(a) - \gamma_{SL,CRC} x_{SL}(a) - \mu(a) x_{SL}(a)$$

$$\frac{dx_{CRC1}(a)}{da} = \gamma_{AA,CRC1} x_{AA}(a) + \gamma_{SL,CRC1} x_{SL}(a) - \gamma_{CRC1,DC1} x_{CRC1}(a) - \gamma_{CRC1,CRC2} x_{CRC1}(a) - \mu(a) x_{CRC1}(a)$$

$$\frac{dx_{CRC2}(a)}{da} = \gamma_{CRC1,CRC2} x_{CRC1}(a) - \gamma_{CRC2,DC2} x_{CRC2}(a) - \gamma_{CRC2,CRC3} x_{CRC2}(a) - \mu(a) x_{CRC2}(a)$$

$$\frac{dx_{CRC3}(a)}{da} = \gamma_{CRC2,CRC3} x_{CRC2}(a) - \gamma_{CRC3,DC3} x_{CRC3}(a) - \gamma_{CRC3,CRC4} x_{CRC3}(a) - \mu(a)\, x_{CRC3}(a)$$

$$\frac{dx_{CRC4}(a)}{da} = \gamma_{CRC3,CRC4} x_{CRC3}(a) - \gamma_{CRC4,DC4} x_{CRC4}(a) - \mu(a) x_{CRC4}(a)$$

$$\frac{dx_{DCi}(a)}{da} = \gamma_{CRCi,DCi} x_{CRCi}(a) - \gamma_{DCi,Death} x_{DCi}(a) - \mu(a) x_{DCi}(a), \quad i=1,2,3,4$$

where $\mu(a)$ was the non-CRC mortality rate at age a (based on data from the Hong Kong Census and Statistics Department; https://www.censtatd.gov.hk). We inferred the prevalence of each disease stage s at age 20 years ($x_s(20)$) and the progression rates (ie, $\gamma_{s,s'}$) from the screening data. In this cohort simulation, disease prevalence among individuals who had never been diagnosed with CRC was $p(s|a,\theta) = \frac{x_s(a)}{\sum_{s\in W} x_s(a)}$, where $W=\{N,HP,NA,SL,AA,CRC\}$. We assumed that the incidence of CRC diagnosis among screenees would have been identical to the incidence in the general population if no screening had been conducted. We also assumed that if an individual had disease stage s, the probability density function (pdf) of his/her two-sample FIT values, $f(\cdot|s,\theta)$, was independent of age.

Let C_k^+ and C_k^- be the set of screenees in the dataset with and without colonoscopy diagnosis in the k^{th} round of FIT screening, respectively. Because the Hong Kong Cancer Registry (HKCaR) reported cancer data with 5-year age bands, we aggregated cancer incidence for the same age groups in our cohort simulation during formulation of the likelihood function. We used HKCaR 2012-2016 data for statistical inference. Let z_j be the total number of CRC cases in the j^{th} age group during 2012-2016, as recorded by the HKCaR, and λ_j be the probability that an individual would be diagnosed with CRC when he/she was in the j^{th} age group in the cohort simulation. The likelihood function was

$$L(\theta) = \underbrace{\prod_{i\in C_1^+} p(s_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i1}}|s_{i1},\theta)}_{\text{First-time screenees who were FIT}_2\text{-positive and had received a colonoscopy diagnosis } (s_{i1})} \times \underbrace{\prod_{i\in C_2^+} \sum_{s_{i1}\in W} p(s_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i1}}|s_{i1},\theta)\pi(s_{i1},s_{i2},a_{i2}-a_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i2}}|s_{i2},\theta)}_{\text{Repeat screenees who were FIT}_2\text{-positive in the second round of FIT screening and had received a colonoscopy diagnosis } (s_{i2})} \times \underbrace{\prod_{i\in C_2^-} \sum_{s_{i1},s_{i2}\in W} p(s_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i1}}|s_{i1},\theta)\pi(s_{i1},s_{i2},a_{i2}-a_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i2}}|s_{i2},\theta)}_{\text{Repeat screenees who did not receive a colonoscopy diagnosis in either round of FIT screening}} \times \underbrace{\prod_j Poisson(z_j, N\lambda_j)}_{\substack{\text{CRC incidence data from}\\ \text{Hong Kong Cancer Registry}}} \times \underbrace{\prod_j \frac{exp\left(-60\left(max\{0.1-\xi_j,0\}+max\{\xi_j-0.3,0\}\right)\right)}{D}}_{\substack{\text{Prior probability that 10\% to 30\% of CRC cases in each}\\ \text{1-year age group } j \text{ developed via the serrated lesion pathway}}}$$

where ξ_j was the proportion of diagnosed CRC cases that developed via the serrated pathway in the cohort simulation, and the pdf $\frac{\exp(-60(\max\{0.1-\xi_j,0\}+\max\{\xi_j-0.3,0\}))}{D}$ was used to incorporate the prior information that ξ_j should lie between 10% and 30% (D served as the normalisation constant).[4]

For risk prediction analytics, suppose that a screenee at age a_1 had two-sample FIT values $\boldsymbol{h_1}=(h_1^1,h_1^2)$ in the first round of screening, contingent on θ. Thus, the probability that he/she had disease stage s_1 during the first round of screening would be:

$$P(s_1|\boldsymbol{h_1},a_1,\theta) = \frac{p(s_1|a_1,\theta) f(\boldsymbol{h_1}|s_1,\theta)}{\sum_{u\in W} p(u|a_1,\theta) f(\boldsymbol{h_1}|u,\theta)} \quad (1)$$

Additionally, suppose that this screenee was FIT_2-negative in the first round of screening (ie, $\max(\boldsymbol{h_1})<100$ ng/mL and thus not referred for colonoscopy); the probability that he/she had disease stage s at age $a\geq a_1$ would be:

$$P(s|\boldsymbol{h_1},a_1,a,\theta) = \sum_{s_1} P(s_1|\boldsymbol{h_1},a_1,\theta)\pi(s_1,s,a-a_1|a_1,\theta) \quad (2)$$

before he/she underwent the second round of screening. If the screenee returned to the programme for the second round of screening at age a_2, the probability that he/she was FIT_2-positive would be:

$$P(\text{FIT}_2\text{–positivity}|\boldsymbol{h_1},a_1,a_2,\theta) = \sum_s P(s|\boldsymbol{h_1},a_1,a_2,\theta)\int_{max(\boldsymbol{h_2})>100} f(\boldsymbol{h_2}|s,\theta)d\boldsymbol{h_2} \quad (3)$$

If the FIT_2 values in the second round of screening were $\boldsymbol{h_2}$, the probability that the screenee had disease stage s_2 would be updated to:

$$P(s_2|\boldsymbol{h_1},\boldsymbol{h_2},a_1,a_2,\theta) = \frac{P(s_2|\boldsymbol{h_1},a_1,a_2,\theta) f(\boldsymbol{h_2}|s_2,\theta)}{\sum_{u\in W} P(u|\boldsymbol{h_1},a_1,a_2,\theta) f(\boldsymbol{h_2}|u,\theta)} \quad (4)$$

We used the c-statistic to evaluate the predictive power of equations 3 and 4. Specifically, the dataset for equation 3 comprised the FIT_2 values of all repeat screenees, whereas the dataset for equation 4 comprised the disease stages of all repeat screenees who had received a colonoscopy diagnosis.

Results

The complete dataset consisted of screening data from 71 346 men and 91 570 women aged 53 to 77 years who had received FIT screening reports from the Hong Kong Colorectal Cancer Screening Programme by 27 March 2020. Among these participants, 6920 men and 8050 women were repeat screenees who were FIT_2-negative in the first round, returned for a second round of screening after 2 years, and had second-round screening reports.

The fitted model was consistent with the data (Fig 1). We estimated that at age 20 years, >99% of individuals were free of any colorectal polyps or lesions. For both men and women, the annual incidence rate of developing non-advanced adenoma via the conventional adenoma pathway increased between age 20 and 80 years, with median peaks at age 80 years of 9.1% (95% credible interval [CrI]=5.6-13.2%) in men and 9.7% (95% CrI=7.5-12.4%) in women. The age-specific incidence rate of developing hyperplastic polyps via the serrated pathway followed a similar trend, with an earlier peak at age 70 years and a 70% to 75% decrease in magnitude: 2.3% (95% CrI=1.4-3.0%) in men and 3.0% (95% CrI=2.2-3.7%) in women.

The annual progression rates of AA to (undiagnosed) CRC were 5.9% (95% CrI=5.4-6.3%) in men and 6.4% (95% CrI=5.7-7.5%) in women; the corresponding rates of SL to CRC were 3.1% (95% CrI=2.7-3.5%) and 1.9% (95% CrI=1.6-2.3%). The respective mean durations of preclinical stage 1-4 CRC were 2.8, 3.0, 0.58, and 1.0 years in men and 4.2, 1.7, 0.44, and 2.4 years in women. Figure 2 shows the estimated age-specific prevalences in different disease stages in the fitted natural history model.

After adjustments for sampling and measurement errors, we estimated the median maximum FIT_2 value (ie, the determinant for colonoscopy referral) for individuals in each health state. The estimates suggested that FIT_2 values among individuals with SL/AA/CRC are generally lower in

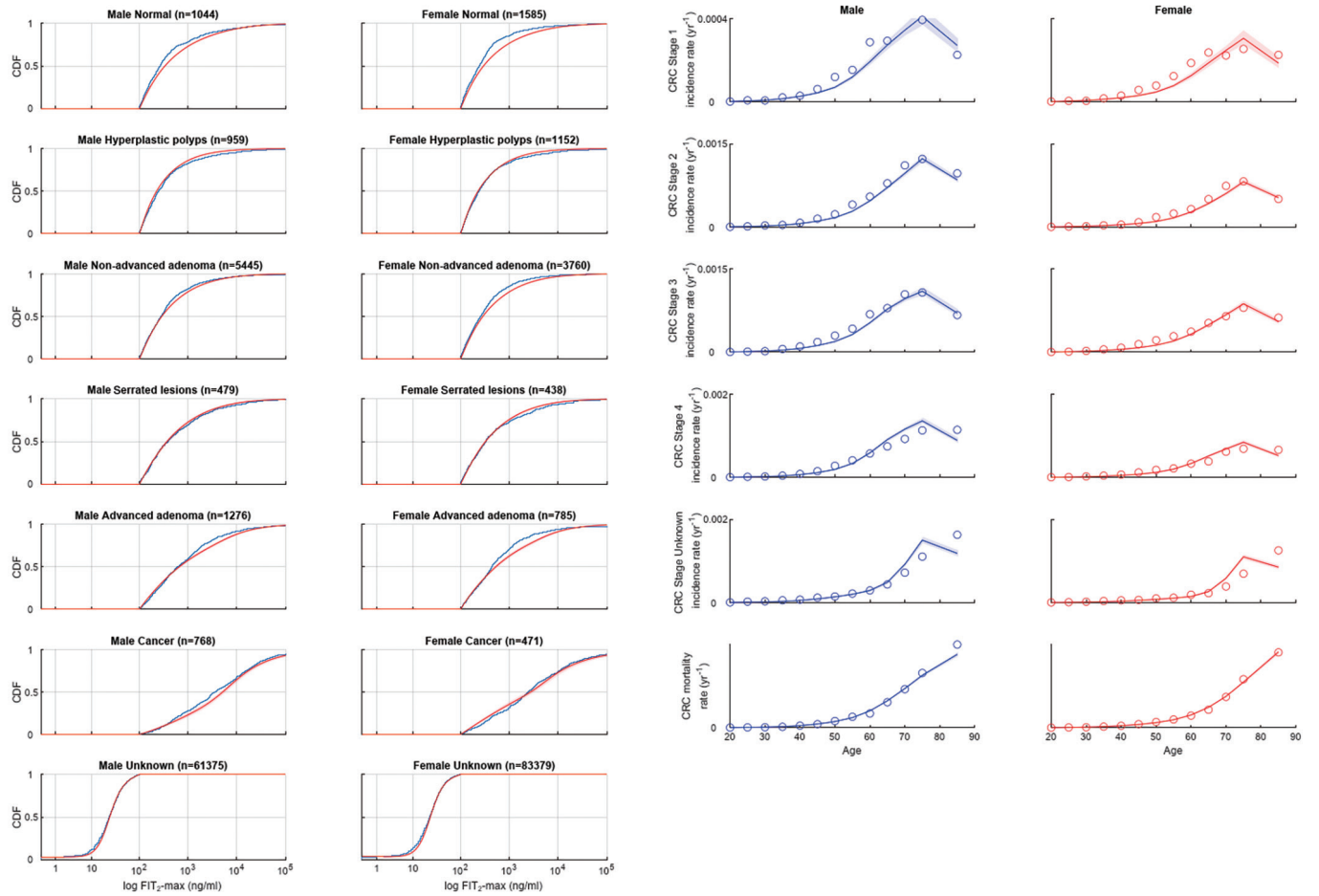

FIG 1. Goodness-of-fit of the fitted model. First two columns show cumulative distribution functions of FIT_2 values, stratified by colonoscopy outcomes. Blue lines represent empirical data, and red lines represent fitted models. Third and fourth columns show age-specific incidence (stratified by stage at diagnosis) and mortality rate of colorectal cancer, respectively. Circles represent empirical data. Lines represent median fitted values. Shaded regions represent corresponding 95% credible intervals.

Abbreviations: CDF, cumulative density function; CRC, colorectal cancer; FIT_2, two-sample faecal immunochemical test.

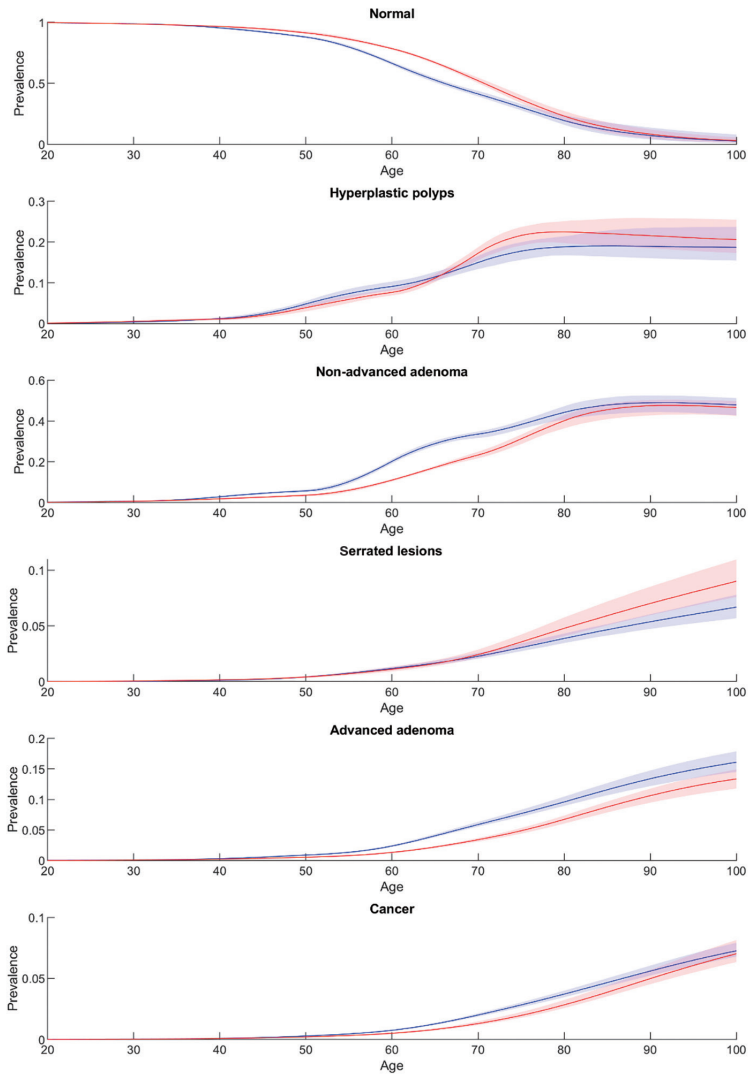

FIG 2. Estimated age-specific prevalences in different disease stages in the fitted natural history model. Blue and red lines represent results for men and women, respectively. Shaded regions represent corresponding 95% credible intervals.

women than in men. Using a positivity threshold of 100 ng/mL for the detection of CRC, we found that FIT_2 had sensitivities of 92% (95% CrI=90-94%) in men and 71% (95% CrI=66-75%) in women; using the same positivity threshold for the detection of SL/AA/CRC, FIT_2 had sensitivities of 58% (95% CrI=56-60%) in men and 47% (95% CrI=45-49%) in women (Fig 3). For the detection of CRC or SL/AA/CRC, FIT_2 had specificities of approximately 85% in men and 90% in women.

To assess the predictive power of equations 3 and 4, we used a dataset consisting of 6920 male and 8050 female repeat screenees. Among them, 12.2% and 8.2% were FIT_2-positive and had been referred for colonoscopy. The corresponding percentages predicted by equation 3 (which projected disease progression for approximately 2 years, based on the probability distribution of disease stages inferred from first-round FIT_2 values) were 16.2% and 11.8%. The c-statistics of equation 3 for predicting second-round FIT_2 positivity among repeat screenees, based on their first-round FIT_2 values, were 0.52 (95% CrI=0.51-0.54) for men and 0.5 (95% CrI=0.48-0.52) for women. These results indicate that equation 3 had very limited predictive power in predicting FIT_2 positivity among repeat screenees at the individual level.

The repeat screenees included 750 men and 582 women who were FIT_2-positive in second-round screening and had colonoscopy results. Among them, 2.9% of men and 2.2% of women had been diagnosed with CRC; 19.0% of men and 15.6% of women had been diagnosed with advanced colorectal diseases (SL/AA/CRC). The corresponding percentages predicted by equation 4 were 2.3% and 2.5% for CRC and 15.3% and 13.5% for advanced colorectal diseases. The c-statistics of equation 4 for predicting CRC from both-round FIT_2 values were 0.73 (95% CrI=0.57-0.84) for men and 0.83 (95% CrI=0.67-0.92) for women. The c-statistics of equation 4 for predicting SL/AA/CRC were 0.61 (95% CrI=0.55-0.66) for men and 0.60 (95% CrI=0.53-0.66) for women. These results indicate that equation 4 had moderate power in predicting advanced colorectal diseases from both rounds of FIT_2 values (based on the fitted natural history model).

Discussion

In Hong Kong, biennial FIT screening has been included in routine management for individuals aged 50 to 75 years. We developed new analytics to characterise the epidemiology and natural history of CRC in Hong Kong. The findings may help to optimise the CRC screening programme.

First, the current CRC screening programme uses a uniform threshold for FIT positivity, regardless of age and sex. Our fitted model showed that FIT values among individuals diagnosed with advanced colorectal diseases were generally lower in women than in men. This finding suggests that the use of sex-specific FIT positivity thresholds, which have been implemented in the CRC screening programme in Stockholm-Gotland (Sweden),[5] would allow comparable test performance (sensitivity and specificity) for the detection of colorectal neoplastic diseases.

Second, our fitted model had moderate power in predicting advanced colorectal neoplastic diseases from FIT values (before colonoscopy), but it had limited power in predicting FIT positivity among repeat screenees. Studies such as the Asia-Pacific Colorectal Screening scoring system have shown that factors such as family history of CRC (in first-degree relatives), smoking history, and body mass index may provide good predictive power for

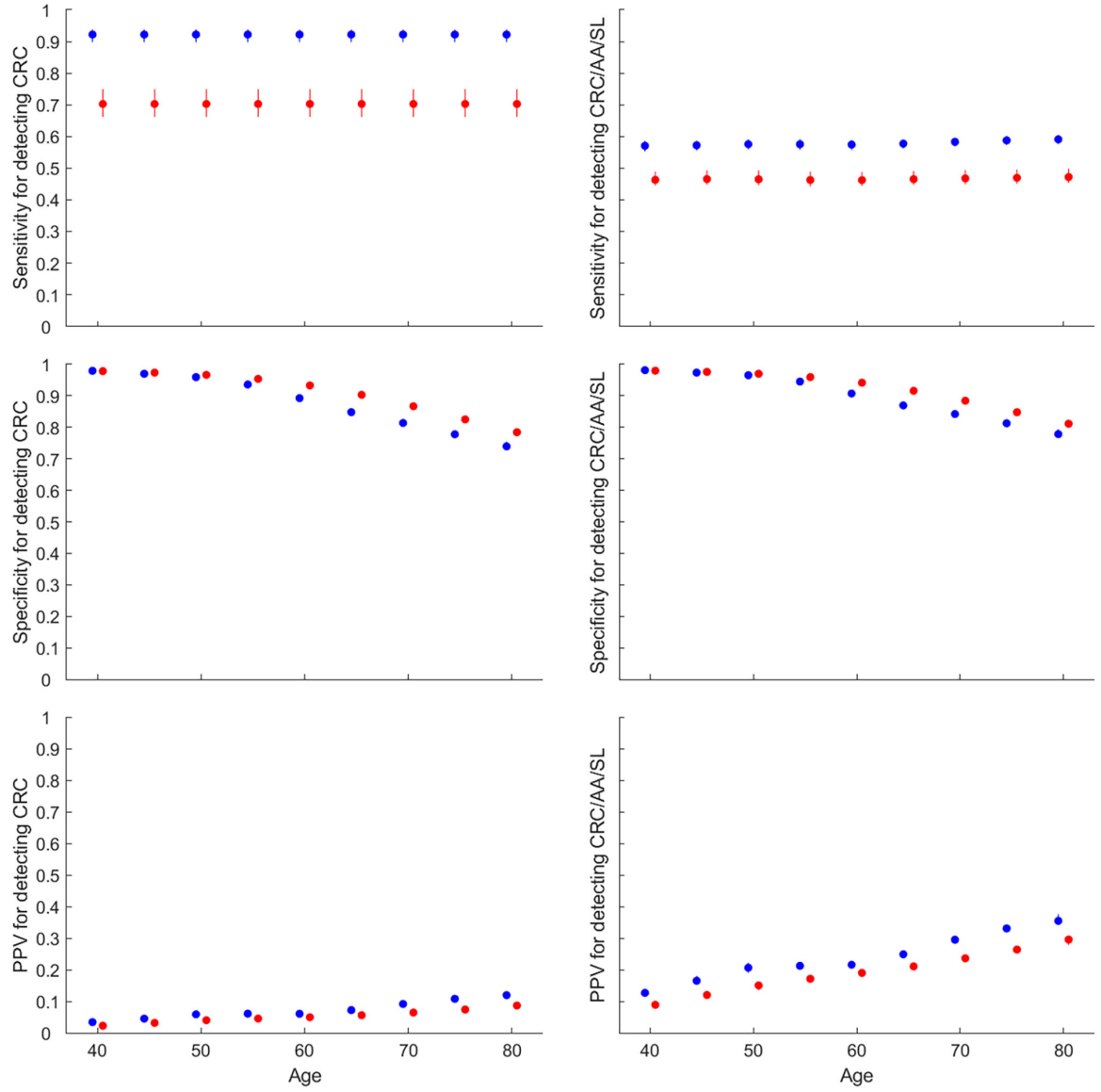

FIG 3. Predictive model performance. Blue and red dots represent results for men and women, respectively. Error bars represent corresponding 95% credible intervals.
Abbreviations: AA, advanced adenoma; CRC, colorectal cancer; PPV, positive predictive value; SL, serrated lesions.

advanced neoplasia. Although these data should be readily available in screenees' electronic health records, they are not currently available in the Hong Kong CRC screening programme database and thus could not be included as risk factors in our model. We recommend linking the screening database to screenees' electronic health records to ensure that data regarding CRC risk factors can be accessed to optimise analytics for prediction of advanced neoplasia. The incorporation of risk estimates for individual screenees could also facilitate the development of personalised screening algorithms. For example, screenees with a higher risk of neoplasia may require more frequent screening, whereas individuals with a lower risk of neoplasia may undergo less frequent screening (eg, after consecutive negative FITs).

Third, routine data from FIT screening programmes can be readily used to characterise CRC epidemiology. Our fitted natural history model provides an evidence-based analytical platform for future optimisation of the CRC screening programme. The cost-effectiveness of potential alternative screening algorithms, such as sex-specific FIT positivity thresholds and differences in age range and screening frequency, should be evaluated

by including economic components of healthcare (eg, cost of screening and treatments) in current mathematical simulation models. This type of mechanism has been used to inform CRC screening strategies in other countries such as Australia and the United States.[6,7]

Fourth, participation and compliance with recommended guidelines are important factors for the success of a screening programme. Policymakers should monitor participation and compliance rates, with the goal of providing additional support to underserved populations. Proactive and strategic invitations may help unscreened individuals to engage with the screening programme. The screening process could be optimised by combining the screening database and the centralised electronic health record system.

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