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# Cost-effectiveness of colorectal cancer screening under different scenarios of colonoscopy adherence: a microsimulation study

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## ABSTRACT

**Introduction** Low adherence to colonoscopy has greatly reduced the efficiency and cost-effectiveness of colorectal cancer (CRC) screening in China. This study aims to examine the cost-effectiveness of five initial tests followed by several scenarios of colonoscopy adherence.

**Methods** A microsimulation model was constructed to compare the parallel use of risk assessment and two-specimen faecal immunochemical test (FIT) (currently used method in Shanghai) and several assumed initial tests (one-specimen FIT, two-specimen FIT, and risk scoring systems (RSS) incorporating one-specimen or two-specimen FIT) under adherence of observed levels, 50%, 60%, 70%, 80% or 90% among 100 000 individuals aged 50–74 years. Incremental cost-effectiveness ratios (ICERs) were computed using the currently used or the next most effective method as the reference. One-way and probabilistic sensitivity analyses were performed to assess the robustness of the findings.

**Results** The RSS incorporating two-specimen FIT was more effective in reducing CRC incidence and mortality at colonoscopy adherence levels below 80%, whereas the currently used method performed better at higher adherence levels. The currently used method was effective and cost-effective for CRC screening, with an ICER relative to the next most effective method ranging from 153.000 to 29 165.120 CNY per quality-adjusted life-year. Enhancing adherence to colonoscopy increased the detection of early-stage CRC and improved the cost-effectiveness ratio and ICER of the current method. The current method had a probability of 35.5%, 34.5%, 35.5%, 40.0%, 32.0% and 38.0% for being the optimal strategy at observed level, 50%, 60%, 70%, 80% and 90% adherence, respectively, all within a willingness-to-pay threshold of 1 to 3 times the gross domestic product per capita.

**Conclusions** The parallel use of risk assessment and two-specimen FIT is a cost-effective method for CRC screening in Chinese populations. Enhancing colonoscopy adherence may further improve the effectiveness and cost-effectiveness of the screening programme.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The cost-effectiveness of colorectal cancer (CRC) screening has been evaluated based on assumptions of high colonoscopy adherence (80%–100%), and by considering only the adenoma-carcinoma pathway for the natural history of CRC.

⇒ The influence of varying colonoscopy adherence on the cost-effectiveness of CRC screening remains unclear.

### WHAT THIS STUDY ADDS

⇒ For the first time, we evaluated the effectiveness and cost-effectiveness of five initial screening tests followed by different colonoscopy adherence scenarios through a simulation that incorporated both adenoma-carcinoma and serrated lesions pathways for CRC development.

⇒ The parallel use of faecal immunochemical test (FIT) and questionnaire-based risk assessment (RA) was found to be more effective and most cost-effective across different colonoscopy adherence scenarios, and thereby can be considered the optimal strategy. Enhancing colonoscopy adherence may further improve the incremental cost-effectiveness ratio of this method relative to the next most effective approach.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The parallel use of FIT and RA should be recommended for CRC screening in Chinese populations rather than FIT alone.

⇒ The cost-effectiveness of the CRC screening programme in Shanghai could be further enhanced by improving adherence to colonoscopy.

## INTRODUCTION

Colonoscopy screening has been proven to lower the incidence and mortality of colorectal cancer (CRC)[1] and is applied as a public health service in many countries.[2] Considering the constraints of colonoscopy capacity, a triage screening strategy involving a colonoscopy following a positive faecal immunochemical test (FIT) has

been widely used globally and found to reduce colonoscopy demands by around 30%.[3] Unfortunately, low adherence to subsequent colonoscopy was commonly observed, which has greatly jeopardised the efficiency and cost-effectiveness of CRC screening.[4]

The cost-effectiveness of CRC screening was more likely to be evaluated through modelling studies. Most previous microsimulation models were developed by assuming the adherence to subsequent colonoscopy to be 80%–100%,[5–7] which is much higher than the levels observed in real-world practices.[4] Moreover, most previous models assumed that all CRCs progressed through the adenoma-carcinoma pathway, which was true for 70%–90% of cases, but not for the other 10%–20% cases following the serrated neoplasia pathway and the remaining 2%–7% originating from microsatellite instability.[8] It has been suggested that CRCs derived from serrated lesions involve different genetic and epigenetic variations from those derived from adenomas[9] and are less likely to be screen-detected.[10] Therefore, the serrated neoplasia pathway should be included in microsimulation models to ensure an accurate evaluation of the cost-effectiveness of CRC screening.

In China, the current recommendation for CRC screening is the parallel use of a questionnaire-based risk assessment (RA) and two-specimen qualitative FIT as initial tests, followed by colonoscopy for those positive in the initial tests.[11] This triage screening strategy has achieved a colonoscopy adherence of over 75% in rural areas of Zhejiang Province and has been proven to be effective and cost-effective.[12] However, this strategy resulted in a colonoscopy adherence of only 39.8% among high-risk subjects in Shanghai.[13] A recent microsimulation analysis demonstrated that the parallel use of RA and two-specimen qualitative FIT might be the most cost-effective strategy at colonoscopy adherence of 80% or above, while quantitative FIT performed better under the observed adherence level.[14] However, quantitative FIT has not been widely used in China.

We previously observed higher adherence to colonoscopy when using optimised risk scoring systems (RSS) that incorporate several predictive variables (age, sex, family history of CRC, chronic diarrhoea, mucus or bloody stool and history of any cancer) and one-specimen or two-specimen qualitative FIT results.[15] However, the impact of improved adherence to colonoscopy on cost-effectiveness of CRC screening remains unclear. In this study, we evaluated the effectiveness and cost-effectiveness of the optimised RSS, the currently used method, and qualitative FIT alone under different scenarios of colonoscopy adherence based on the Shanghai CRC Screening Programme.

## MATERIALS AND METHODS

### Overview

A microsimulation model was constructed based on a decision tree and a Markov model to assess the effectiveness and cost-effectiveness of multiple CRC screening strategies in Shanghai, China (online supplemental figure 1). The decision tree was employed to allocate the initial health states of simulated individuals in the Markov model, while the Markov model was designed to simulate the incidence and progression of CRC under different screening strategies and colonoscopy adherence scenarios.[16] The screening strategies altered the distributions of simulated individuals across different health states but did not influence the transition probabilities between health states in the Markov model. This model-based economic evaluation was performed from a healthcare-sector perspective using TreeAge Pro 2022 (Williamstown, Massachusetts). The study was reported following the Consolidated Health Economic Evaluation Reporting Standards (online supplemental table 1).[17]

### The Shanghai CRC Screening Programme

The Shanghai CRC Screening Programme was an ongoing organised screening programme initiated in 2013.[13] All residents aged 50–74 years without prior CRC were eligible to participate, and volunteers were consecutively enrolled in the programme. A total of 826 445 eligible subjects were enrolled in 2013.[15] The programme adopted a questionnaire-based RA and two-specimen qualitative FIT as initial screening tests, followed by colonoscopy for subjects who tested positive in RA or any FIT. Participants were considered positive in RA if they had one of the three events: (1) history of any cancer; (2) history of colorectal polyps; (3) CRC in first-degree relatives and/or at least two of the following: (1) history of chronic constipation; (2) history of chronic diarrhoea; (3) history of mucus or bloody stool; (4) serious life events (eg, loss of a family member); (5) chronic appendicitis or appendectomy and (6) chronic cholecystitis or cholecystectomy.

All participants were instructed to collect two faecal specimens 1 week apart. The specimens were collected in tubes containing about 5 mL of moist faeces and were required to be returned to a local hospital within 48 hours. FIT results were read within 5 min using a colloidal gold assay, with a positivity threshold of 100 ng Hb/mL (20 µg Hb/g faeces).[15] Subjects who tested positive in RA or any FIT were identified as high-risk individuals, required to attend a colonoscopy examination and invited to repeat the initial screening in the second year if no CRC was detected. Those who tested negative in the initial screening tests were considered low-risk and were recommended for triennial screening.[5]

### Simulated population

A simulated population of 100 000 individuals at an average risk of CRC was generated through Monte Carlo simulation. The simulated individuals were aged 50–74 years and without prior CRC, similar to the participants in the Shanghai CRC Screening Programme.[13 15] The starting age of screening was set according to the age distribution of participants in the Shanghai CRC Screening Programme in 2013. Individuals were assumed

to enter the model and follow the alternative screening strategies (online supplemental figure 2).

## Microsimulation model

The Markov model was constructed based on the Adenoma and Serrated pathway to Colorectal Cancer (ASCCA) model and the Policy1-Bowel model to simulate the natural history of CRC over a lifetime horizon under different screening scenarios.[18–20] The conventional adenoma-carcinoma and serrated neoplasia pathways were simulated to account for 85% and 15% of all CRC cases, respectively (online supplemental figure 3).[5] It was assumed that precancerous lesions could be screen-detected and treated earlier by polypectomy. Due to the absence of a uniform guideline on postpolypectomy surveillance colonoscopy in China, surveillance colonoscopy was integrated into the model according to the European surveillance guideline.[21] Specifically, individuals with advanced adenomas (≥10 mm in size, with villous components or high-grade dysplasia), large hyperplastic polyps or sessile serrate lesions (≥10 mm in size) were scheduled to every 3-year colonoscopy until negative results were obtained. No follow-up was simulated for individuals with non-advanced adenomas and small hyperplastic polyps or sessile serrated lesions, who were modelled to return to no lesion after polypectomy and continue undergoing screening. Preclinical CRCs were assumed to be detected either through symptoms or screening and then treated. CRC cases surviving for 5 years after diagnosis and treatment were considered to have no additional risk of death from cancer compared with those without CRC.[20] All health states were modelled as Markov states with a yearly time-step, and individuals were followed until death or life expectancy according to the China-specific life table data in 2013.[22] There were two additional assumptions in the established model: (1) adherence to initial screening tests was 100% and (2) regression of hyperplastic polyps and sessile serrated lesions was considered in addition to progression to high-grade lesions. Half-cycle correction was applied to avoid overestimation of expected costs and effectiveness.

## Model parameters

### Natural history of CRC

The initial distributions of simulated individuals across different health states by age at screening were derived from the baseline screening results of the Shanghai Screening Programme in 2013 and previous reports,[5 6] or based on rational assumptions (online supplemental table 2). Due to the lack of parameters on the natural history of serrated lesions in Chinese populations, transition probabilities and stage-specific mortality were obtained through literature searches. For the sex-specific parameters, we estimated the weighted probabilities using the sex ratio of 4:6 (male: female) in the Shanghai CRC Screening Programme. To ensure the robustness of the model, significant and invalid parameters were calibrated against the target data, which included age-specific CRC incidence (online supplemental figure 4) and the stage distribution of symptom-detected CRC cases (online supplemental figure 5) prior to the introduction of screening. The age-specific natural background mortality was extracted from the China Population and Employment Statistics Yearbook, 2020 (online supplemental table 3).[23]

### Screening strategies

We defined the currently used initial tests followed by colonoscopy as the reference screening strategy and investigated four assumed initial tests: (1) one-specimen qualitative FIT; (2) two-specimen qualitative FIT; (3) RSS incorporating one-specimen qualitative FIT and (4) RSS incorporating two-specimen qualitative FIT previously developed.[15] The sensitivities and specificities of initial tests and colonoscopy, as well as the probabilities of colonoscopy complications, were obtained from the Shanghai Screening Programme[15] or through literature searches (online supplemental table 4).

### Adherence to colonoscopy

The adherence to colonoscopy in the Shanghai Screening Programme was regarded as observed levels: 39.5% for the currently used method, 47.2% for one-specimen FIT, 46.7% for two-specimen FIT, 43.2% for RSS incorporating one-specimen FIT and 45.4% for RSS incorporating two-specimen FIT. We further investigated the cost-effectiveness of screening under colonoscopy adherence scenarios of 50%, 60%, 70%, 80% and 90%, and assumed an adherence of 80% to surveillance colonoscopy, in line with a previous study.[14]

### Costs and utility scores

The costs of screening and treatment were obtained from the studies in China[5] and other Asian countries[24] (online supplemental table 5), which were presented in Chinese Yuan (CNY) and converted to the prices in 2021 based on the Consumer Price Index.[25] The effectiveness of screening was evaluated using utility-weighted life expectancy expressed as quality-adjusted life-year (QALY). Since no utility scores for serrated lesions were reported, the utility scores for small and large serrated lesions were assumed to be similar to those for non-advanced and advanced adenomas, respectively. Future costs and QALYs were discounted at 5% per year.[26]

## Statistical analysis

### Effectiveness and cost-effectiveness analysis

Microsimulation was performed to predict the lifetime outcomes of CRC incidence, CRC-related deaths, costs, QALYs, health resource utilisation and potential harms. Strategies that gained fewer QALYs at a higher cost than any other strategy were considered dominated; otherwise, the strategies were considered undominated. Specifically, the strategies that gained more QALYs at a lower cost than any other strategy dominate. Cost-effectiveness ratios (CERs) were calculated for each strategy as the costs per capita (in CNY) divided by the effectiveness per capita (in

QALYs). The incremental CERs (ICERs) were computed by dividing the difference in costs (incremental costs) by the difference in QALYs gained (incremental QALYs) for each strategy relative to either the currently used method (status quo) or the next most effective strategy (ie, the most cost-effective strategy among the remaining less costly options). The optimal strategy at each colonoscopy adherence scenario was identified through pairwise comparisons between each strategy and the next most effective strategy.

Due to the lack of a widely accepted willingness-to-pay threshold in Chinese populations, we set the threshold at CNY84 833 according to the gross domestic product (GDP) per capita in China in 2021.[27] We adopted the WHO definition for cost-effectiveness: highly cost-effective if the ICER is below the GDP per capita; cost-effective if the ICER is between 1 and 3 times the GDP per capita; and not cost-effective if the ICER is higher than 3 times the GDP per capita.[28]

### Sensitivity analysis

To assess the robustness of the results, we performed one-way deterministic and probabilistic sensitivity analyses. For deterministic sensitivity analyses, we varied key parameters within their plausible ranges using standard distributions for 10 000 iterations to identify major sensitive parameters. Probabilistic sensitivity analyses were conducted using 200 second-order Monte Carlo simulations with 10 000 iterations to determine the probability of each screening strategy being optimal compared with others in a setting where probabilities, costs and utilities were simultaneously varied.

## RESULTS

### Effectiveness and cost-effectiveness analysis

As shown in table 1, both incident cases and deaths of CRC decreased with increasing colonoscopy adherence by using any of the five screening methods. The number of incident cases was the lowest when applying the RSS incorporating two-specimen at a colonoscopy adherence of 70% or below, and when using the currently used method (parallel use of RA and two-specimen FIT) at an adherence of above 70%. Both the two methods achieved a higher detection rate of early-stage cancer. Moreover, the RSS incorporating two-specimen FIT consistently resulted in the fewest CRC deaths and led to more reduction in CRC incidence (only when adherence below 80%) and mortality than the currently used method.

As presented in table 2, the CER for the currently used method remained the highest across all colonoscopy adherence scenarios. At the observed levels of colonoscopy adherence, the ICER relative to the currently used method was lowest for one-specimen FIT (−2219.352 CNY/QALY) and highest for RSS incorporating two-specimen FIT (153 000 CNY/QALY). Both values were below the GDP per capita and considered highly cost-effective. When adherence was increased to 50% or above, the ICER for two-specimen FIT relative to the currently used method consistently remained the lowest. Compared with the next most effective method, the currently used method was found to be the most cost-effective under different adherence scenarios.

Online supplemental table 6 presents the estimated health resource utilisation and colonoscopy-related complications for alternative screening strategies. The costs for questionnaire-based RA, FITs and colonoscopies were consistently highest for the currently used method and increased with rising colonoscopy adherence. Specifically, if colonoscopy adherence increased from 39.5% to 90%, the colonoscopy load would jump from 55 390 to 124 105, and colonoscopy-related complications would rise from 313 to 635.

As illustrated in figure 1, the currently used method and one-specimen FIT were consistently undominated under different colonoscopy adherence scenarios. RSS incorporating one-specimen FIT became undominated at adherence levels above 60%, and RSS incorporating two-specimen FIT became undominated at adherence levels above 80%. Compared with other strategies on the cost-effective frontier, the currently used method was more effective, yielded an ICER below the GDP per capita and appeared to be most cost-effective under all adherence scenarios.

### Sensitivity analysis

The lower and upper limits of ICERs for other initial tests relative to the currently used method under different scenarios are shown in online supplemental table 7. 10 model parameters were found to be most sensitive, including six test characteristics, two transition probabilities, CRC mortality and the discount rate. At the observed levels of colonoscopy adherence, RSS incorporating two-specimen FIT was less effective and less costly than the currently used method, while the other initial tests were more effective and less costly. When adherence was increased to 50% or above, the ICERs of other tests relative to the currently used method ranged from −5861.390 to 65 316.785 CNY/QALY, all of which were below the GDP per capita.

Regardless of colonoscopy adherence, one-way sensitivity analyses showed a similar ranking of ICER to the base-case analysis. Tornado diagrams of the top 10 parameters influencing the ICERs of RSS incorporating two-specimen FIT versus the currently used method are presented in figure 2. The most sensitive parameter was the transition probability from non-advanced to advanced adenoma when colonoscopy adherence was below 60%, and it became the transition probability from advanced adenoma to CRC at the adherence levels of 60% and 90%, and the discount rate at the adherence levels of 70% and 80%.

For a willingness-to-pay threshold of 1–3 times GDP per capita, the currently used method was consistently found to be most cost-effective at the observed adherence level, 50%, 60%, 70%, 80% and 90%, with the probability

**Table 1** Estimated colorectal cancer cases and deaths using five initial tests followed by varied colonoscopy adherence over the lifetime of 100 000 individuals

| Colonoscopy adherence | CRC cases in 100 000 individuals | Incidence reduction (%) | CRC cases detected (%) | Early-stage CRC (%)* | CRC-related deaths in 100 000 individuals | Mortality reduction (%) |
|---|---|---|---|---|---|---|
| Observed levels | | | | | | |
| One-specimen FIT (47.2%) | 1114 | 1.59 | 791 (71.01) | 64.48 | 292 | 4.26 |
| RSS incorporating one-specimen FIT (43.2%) | 1152 | −1.77 | 818 (71.01) | 64.67 | 299 | 1.97 |
| Two-specimen FIT (46.7%) | 1186 | −4.77 | 862 (72.68) | 69.03 | 272 | 10.82 |
| RSS incorporating two-specimen FIT (45.4%) | 1076 | 4.95 | 816 (75.84) | 68.38 | 215 | 29.51 |
| RA and two-specimen FIT (parallel) (39.5%) | 1132 | NA | 850 (75.09) | 67.53 | 305 | NA |
| Improved to 50% | | | | | | |
| One-specimen FIT | 1068 | 0.84 | 786 (73.6) | 62.47 | 331 | −7.12 |
| RSS incorporating one-specimen FIT | 1096 | −1.76 | 818 (74.64) | 64.06 | 314 | −1.62 |
| Two-specimen FIT | 1155 | −7.24 | 883 (76.45) | 66.25 | 309 | 0.00 |
| RSS incorporating two-specimen FIT | 1015 | 5.76 | 729 (71.82) | 73.53 | 237 | 23.30 |
| RA and two-specimen FIT (parallel) | 1077 | NA | 857 (79.57) | 70.25 | 309 | NA |
| Improved to 60% | | | | | | |
| One-specimen FIT | 1066 | −3.00 | 839 (78.71) | 66.75 | 288 | −8.68 |
| RSS incorporating one-specimen FIT | 1101 | −6.38 | 848 (77.02) | 68.16 | 285 | −7.55 |
| Two-specimen FIT | 1167 | −12.75 | 911 (78.06) | 72.23 | 280 | −5.66 |
| RSS incorporating two-specimen FIT | 1018 | 1.64 | 754 (74.07) | 77.98 | 207 | 21.89 |
| RA and two-specimen FIT (parallel) | 1035 | NA | 850 (82.13) | 74.94 | 265 | NA |
| Improved to 70% | | | | | | |
| One-specimen FIT | 1008 | −0.40 | 785 (77.88) | 68.15 | 288 | −8.68 |
| RSS incorporating one-specimen FIT | 1032 | −2.79 | 788 (76.36) | 69.80 | 285 | −7.55 |
| Two-specimen FIT | 1106 | −10.16 | 881 (79.66) | 73.78 | 280 | −5.66 |
| RSS incorporating two-specimen FIT | 947 | 5.68 | 718 (75.82) | 79.11 | 207 | 21.89 |
| RA and two-specimen FIT (parallel) | 1004 | NA | 837 (83.37) | 74.07 | 265 | NA |
| Improved to 80% | | | | | | |
| One-specimen FIT | 1008 | −7.81 | 783 (77.68) | 65.64 | 253 | −3.27 |
| RSS incorporating one-specimen FIT | 1018 | −8.88 | 791 (77.70) | 68.02 | 269 | −9.80 |
| Two-specimen FIT | 1122 | −20.00 | 903 (80.48) | 71.87 | 256 | −4.49 |
| RSS incorporating two-specimen FIT | 952 | −1.82 | 720 (75.63) | 77.92 | 189 | 22.86 |
| RA and two-specimen FIT (parallel) | 935 | NA | 792 (84.71) | 73.74 | 245 | NA |
| Improved to 90% | | | | | | |
| One-specimen FIT | 1004 | −15.01 | 743 (74.00) | 68.51 | 263 | −15.35 |
| RSS incorporating one-specimen FIT | 1031 | −18.10 | 762 (73.91) | 71.39 | 263 | −15.35 |
| Two-specimen FIT | 1130 | −29.44 | 868 (76.81) | 76.15 | 283 | −24.12 |
| RSS incorporating two-specimen FIT | 949 | −8.71 | 734 (77.34) | 75.89 | 185 | 18.86 |
| RA and two-specimen FIT (parallel) | 873 | NA | 725 (83.05) | 78.62 | 228 | NA |

*Stage I/II CRC.
CRC, colorectal cancer; FIT, faecal immunochemical test; NA, not applicable; RA, risk assessment; RSS, risk scoring system.

of being the optimal strategy at 35.5%, 34.5%, 35.5%, 40.0%, 32.0% and 38.0%, respectively (figure 3).

Online supplemental figure 6 shows the incremental cost and effectiveness scatterplots of RSS incorporating two-specimen FIT relative to currently used method. Under all simulated adherence scenarios, more red dots (more than 50%) were observed at the left top of the willingness-to-pay line (less effective, more costly) than the green dots at the right bottom, showing a higher probability of the currently used method to be more

**Table 2** Base-case cost-effectiveness results for five initial tests followed by varied colonoscopy adherence among 100 000 individuals

| Colonoscopy adherence | Cost per capita (CNY) | Incremental cost (CNY) | | Effectiveness per capita (QALY) | Incremental QALY | | ICER (vs current method, CNY/QALY) | ICER (vs next most effective method, CNY/QALY) |
|---|---|---|---|---|---|---|---|---|
| | | vs current method | vs next most effective method | | vs current method | vs next most effective method | | |
| Observed levels | | | | | | | | |
| One-specimen FIT (47.2%) | 186.674 | −191.446 | NA | 10.636 | 0.086 | NA | Dominate | NA |
| RSS incorporating one-specimen FIT (43.2%) | 218.778 | −159.342 | 32.105 | 10.640 | 0.090 | 0.004 | Dominate | 7989.328 |
| Two-specimen FIT (46.7%) | 272.352 | −105.768 | 53.574 | 10.633 | 0.083 | −0.007 | Dominate | Dominate |
| RSS incorporating two-specimen FIT (45.4%) | 373.530 | −4.590 | 154.752 | 10.520 | −0.030 | −0.120 | 153.000 | Dominated |
| RA and two-specimen FIT (parallel) (39.5%) | 378.120 | NA | 4.590 | 10.550 | NA | 0.030 | NA | 153.000 |
| Improved to 50% | | | | | | | | |
| One-specimen FIT | 215.734 | −160.565 | NA | 10.691 | −0.046 | NA | 3516.164 | NA |
| RSS incorporating one-specimen FIT | 296.436 | −79.864 | 80.702 | 10.691 | −0.045 | 0.001 | 1774.980 | 120 300.749 |
| Two-specimen FIT | 301.112 | −75.187 | 4.677 | 10.690 | −0.046 | −0.001 | 1627.227 | Dominated |
| RSS incorporating two-specimen FIT | 295.387 | −80.912 | −1.049 | 10.708 | −0.029 | 0.016 | 2803.895 | Dominate |
| RA and two-specimen FIT (parallel) | 376.299 | NA | 80.912 | 10.736 | NA | 0.029 | NA | 2803.895 |
| Improved to 60% | | | | | | | | |
| One-specimen FIT | 203.582 | −282.738 | NA | 10.643 | −0.093 | NA | 3044.736 | NA |
| RSS incorporating one-specimen FIT | 256.237 | −230.083 | 52.655 | 10.691 | −0.044 | 0.049 | 5195.203 | 1084.025 |
| Two-specimen FIT | 308.360 | −177.960 | 52.123 | 10.622 | −0.114 | −0.069 | 1565.799 | Dominated |
| RSS incorporating two-specimen FIT | 326.720 | −159.601 | 70.482 | 10.646 | −0.089 | −0.045 | 1785.878 | Dominated |
| RA and two-specimen FIT (parallel) | 486.320 | NA | 159.601 | 10.736 | NA | 0.089 | NA | 1785.878 |
| Improved to 70% | | | | | | | | |
| One-specimen FIT | 266.804 | −300.442 | NA | 10.605 | −0.022 | NA | 13 651.355 | NA |
| RSS incorporating one-specimen FIT | 326.364 | −240.882 | 59.561 | 10.615 | −0.012 | 0.010 | 19 804.932 | 6049.509 |
| Two-specimen FIT | 373.796 | −193.450 | 47.432 | 10.594 | −0.033 | −0.021 | 5842.826 | Dominated |
| RSS incorporating two-specimen FIT | 413.731 | −153.515 | 87.366 | 10.614 | −0.013 | −0.001 | 11 785.037 | Dominated |
| RA and two-specimen FIT (parallel) | 567.246 | NA | 153.515 | 10.627 | NA | 0.013 | NA | 11 785.037 |
| Improved to 80% | | | | | | | | |
| One-specimen FIT | 259.173 | −322.352 | NA | 10.611 | −0.025 | NA | 13 056.529 | NA |
| RSS incorporating one-specimen FIT | 323.862 | −257.662 | 64.690 | 10.623 | −0.013 | 0.012 | 19 987.987 | 5483.059 |
| Two-specimen FIT | 380.851 | −200.674 | 56.989 | 10.612 | −0.024 | −0.011 | 8368.137 | Dominated |

Continued

**Table 2** Continued

| Colonoscopy adherence | Cost per capita (CNY) | Incremental cost (CNY) | | Effectiveness per capita (QALY) | Incremental QALY | | ICER (vs current method, CNY/QALY) | ICER (vs next most effective method, CNY/QALY) |
|---|---|---|---|---|---|---|---|---|
| | | vs current method | vs next most effective method | | vs current method | vs next most effective method | | |
| RSS incorporating two-specimen FIT | 422.855 | −158.670 | 98.993 | 10.629 | −0.007 | 0.006 | 23269.752 | 16302.733 |
| RA and two-specimen FIT (parallel) | 581.525 | NA | 158.670 | 10.636 | NA | 0.007 | NA | 23269.752 |
| Improved to 90% | | | | | | | | |
| One-specimen FIT | 284.223 | −347.564 | NA | 10.639 | −0.019 | NA | 18497.583 | NA |
| RSS incorporating one-specimen FIT | 359.576 | −272.211 | 75.353 | 10.647 | −0.011 | 0.008 | 25353.846 | 9356.865 |
| Two-specimen FIT | 423.912 | −207.874 | 64.336 | 10.636 | −0.022 | −0.011 | 9602.836 | Dominated |
| RSS incorporating two-specimen FIT | 465.538 | −166.248 | 105.963 | 10.652 | −0.006 | 0.005 | 29165.120 | 21040.065 |
| RA and two-specimen FIT (parallel) | 631.786 | NA | 166.248 | 10.657 | NA | 0.006 | NA | 29165.120 |

Strategies that gained fewer QALYs at a higher cost than any other strategy were considered dominated, otherwise the strategies were considered undominated. Specifically, the strategies that gained more QALYs at a lower cost than any other strategy dominate.
CNY, Chinese yuan; CRC, colorectal cancer; FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life-year; RA, risk assessment; RSS, risk scoring system.

cost-effective. The results of sensitivity analyses further confirmed the robustness of base-case results.

## DISCUSSION

In this microsimulation modelling study, we found that the RSS incorporating two-specimen FIT was more effective in reducing CRC incidence and mortality at colonoscopy adherence levels below 80%, while the currently used method (parallel use of RA and two-specimen FIT) performed better at higher adherence levels. Both methods were found to detect more early-stage cancers. The currently used method was the most cost-effective under different colonoscopy adherence scenarios, with the highest CERs and ICERs compared with the next most effective method under almost all scenarios. These results prove the cost-effectiveness of the currently used method in the Shanghai screening programme and highlight the significant benefits of improving adherence to colonoscopy.

In recent years, several microsimulation models have been developed in Western populations by taking the serrated neoplasia pathway into consideration, which included the ASCCA model in Netherlands,[18] the Policy1-Bowel microsimulation model in Australia,[20] the discrete event simulation model in Germany[29] and the MiMiC-Bowel model under development in the UK.[30] Based on the ASCCA model, a simulation study in a Dutch population showed that biennial FIT screening could reduce CRC incidence by 30%, compared with only a 10% reduction with a single colonoscopy.[18] Similarly, a modelling study using Policy1-Bowel microsimulation found that biennial FIT screening was the most cost-effective for CRC screening in Australia, even when colonoscopy adherence decreased from 100% to 71%.[31]

In resource-constrained countries, FIT was usually combined with RA or other tests to identify high-risk individuals for colonoscopy.[32] For example, Sekiguchi *et al*[33] found that personalised screening using a scoring system incorporating age, sex, family history of CRC, body mass index and smoking achieved better effectiveness and cost-effectiveness compared with FIT alone. The Asia-Pacific Colorectal Screening score, which incorporates age, sex, family history of CRC and smoking, can significantly reduce the colonoscopy workload by approximately 50% through triaging low-risk subjects for FIT.[32] However, information on smoking was not collected in the Shanghai CRC Screening Programme, for which head-to-head comparison between the Asia-Pacific Colorectal Screening score and our RA tool was infeasible. In China, the parallel use of FIT and RA has been proved effective and cost-effective in large-scale screening practices,[5 14] likely due to the complementary role of RA in identifying non-bleeding colorectal lesions,[12] including sessile serrated lesions that progress more rapidly and are easily missed by FIT.[34] The parallel use of FIT and RA may increase the sensitivity of screening but has led to low adherence to colonoscopy.[35]

In this study, for the first time, we evaluated the cost-effectiveness of FIT alone and combined with RA by constructing a microsimulation model to simulate the

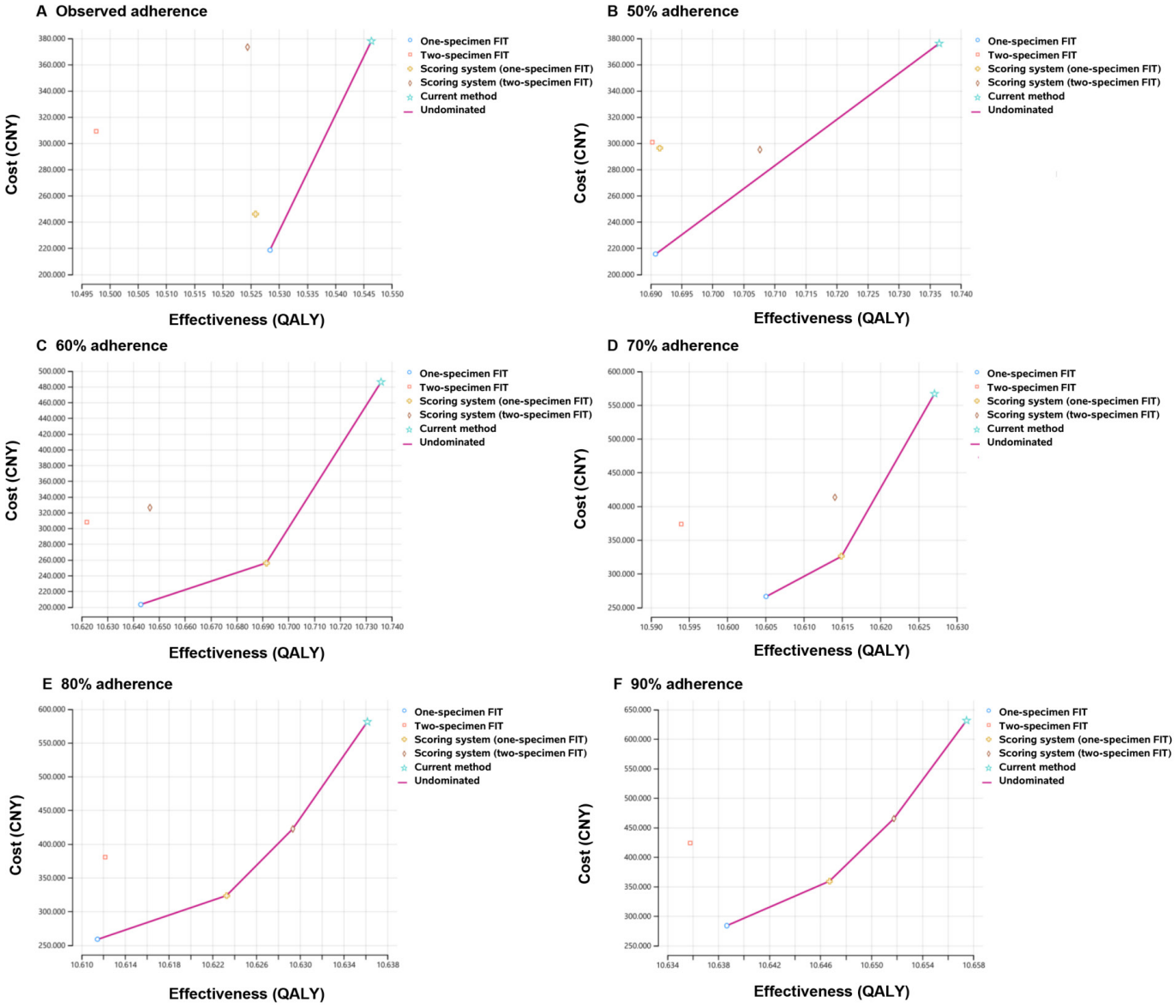


**Figure 1** Cost-effectiveness graph for five initial tests followed by different scenarios of colonoscopy adherence. Strategies on the cost-effective frontier are connected by lines, while strategies above and to the left of the cost-effective frontier are dominated, meaning they are more costly and less effective than alternative strategies. Only the strategies on the cost-effective frontier could be the optimal strategy. The slope of the line connecting two strategies corresponds to the incremental cost-effectiveness ratio. CNY, Chinese yuan; FIT, faecal immunochemical test; QALY, quality-adjusted life year.

natural history of CRC based on both conventional adenomas and serrated lesions pathways. More importantly, we considered multiple adherence scenarios: observed adherence levels, 50%, 60%, 70%, 80% and 90%. We found that the combined use of FIT and RA (either in parallel or as RSS) was more cost-effective than using FIT alone, regardless of adherence to subsequent colonoscopy. These results are consistent with a previous study,[14] highlighting the importance of enhancing colonoscopy adherence to fully achieve the effectiveness and cost-effectiveness of large-scale organised screening programmes.

Evidently, our findings have important public health implications. First of all, the combined use of FIT and RA, either in parallel or as RSS, should be recommended in Chinese populations rather than FIT alone. Our results strongly support the use of RA as a complementary test to FIT due to its low cost and ability to identify individuals with non-bleeding colorectal lesions. Second, colonoscopy adherence in China is currently low, ranging from 14.0% to 55.3%.[13 35 36] In this context, optimising the RA tool based on available predictive variables (eg, RSS incorporating two-specimen FIT) did not achieve substantial benefits in the cost-effectiveness of CRC screening compared with the currently used method. Finally, enhancing colonoscopy adherence in Chinese populations may be more critical to improve the effectiveness and cost-effectiveness of the currently used method. We previously found that selecting initial screening tests with high specificity and positive predictive value may

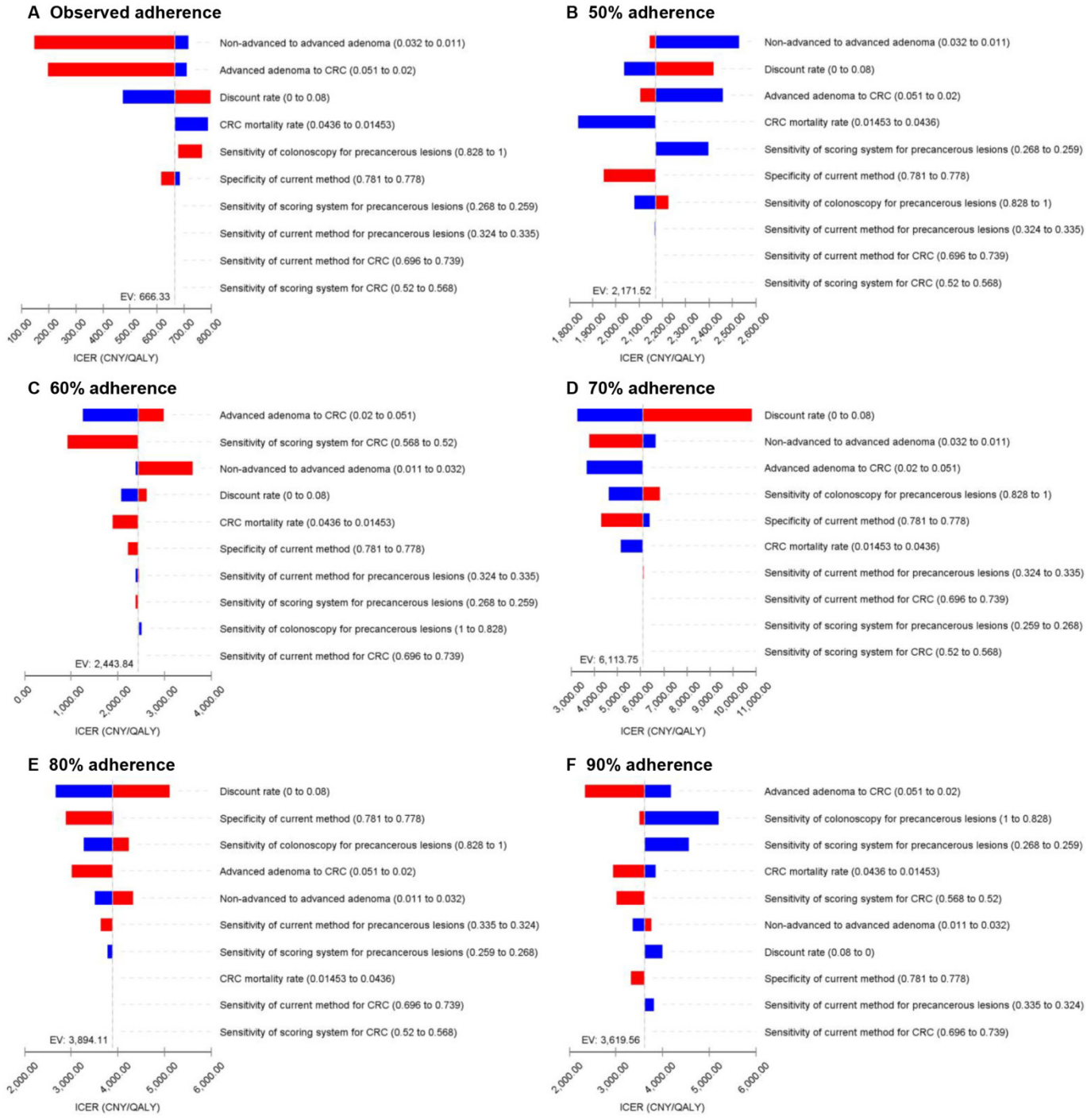


**Figure 2** Tornado diagram of one-way sensitivity analyses for scoring system incorporating two-specimen faecal immunochemical test versus currently used method followed by different scenarios of colonoscopy adherence. CNY, Chinese yuan; CRC, colorectal cancer; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

help improve adherence to subsequent colonoscopy.[4] If colonoscopy adherence is improved to 60% or above, the proportions of detected early-stage cancers could be as high as more than 73%. Thus, the recommended initial test in China, that is, parallel use of RA and FIT, is proved to be the optimal choice.

This study has several strengths. First, the microsimulation model constructed in this study is the first attempt in China to simulate the natural history of CRC based on both conventional adenoma-carcinoma and serrated neoplasia pathways. Our results provide sound evidence for policy decision-making. Second, we examined the cost-effectiveness of CRC screening at different colonoscopy adherence levels, which were often assumed to be high in most previous studies.[5–7] By comparing the cost-effectiveness of five initial tests at observed and assumed levels of colonoscopy adherence, we identified the optimal initial test under the different scenarios, which may facilitate the large-scale implementation of CRC screening. Finally, we used age-specific initial

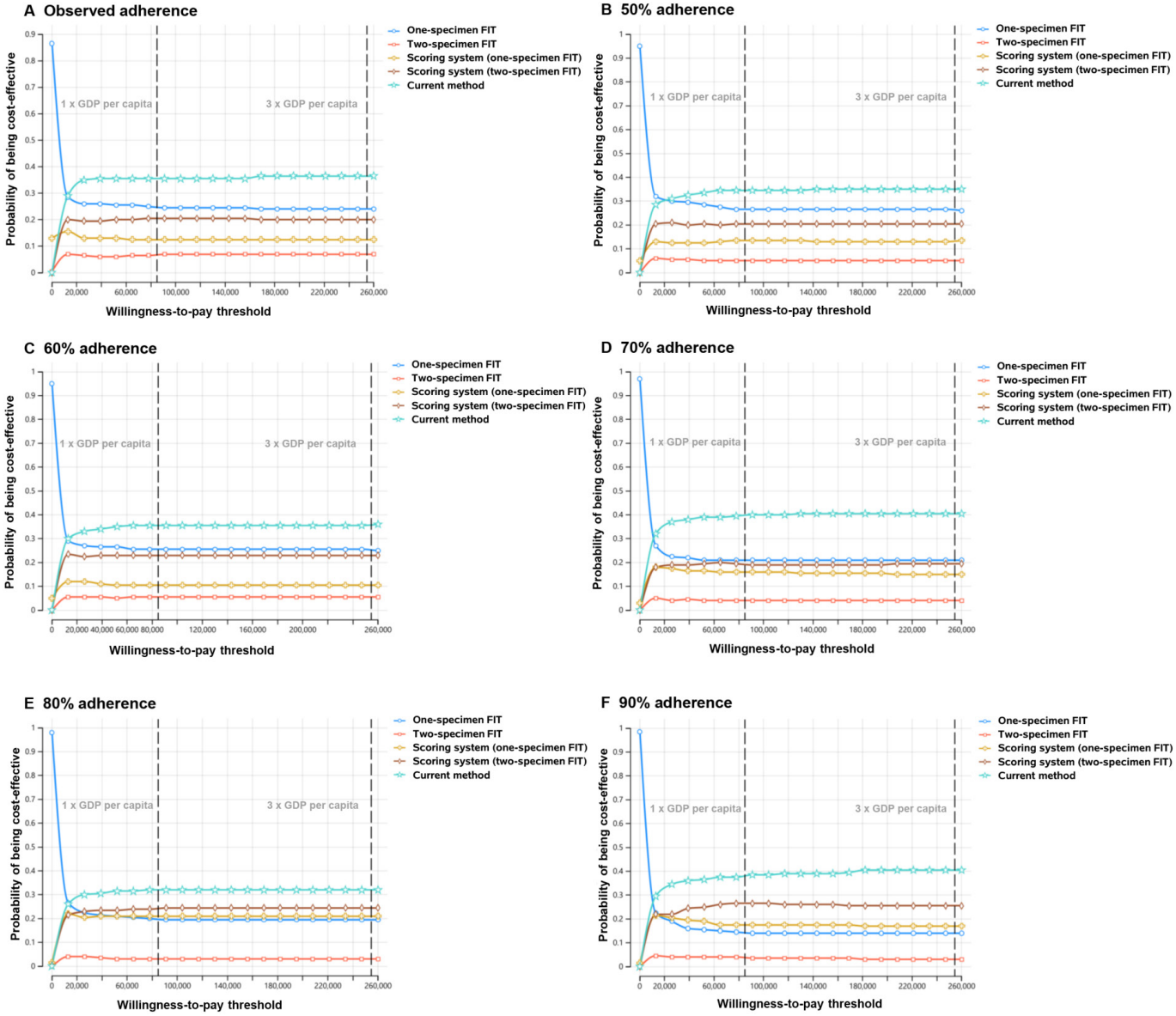


**Figure 3** Cost-effectiveness acceptability curves for five initial tests compared with each other followed by different scenarios of colonoscopy adherence. FIT, faecal immunochemical test; GDP, gross domestic product.

distribution of CRC-related health states, transition probabilities, natural background mortality, and stage-specific mortality of CRC, and incorporated colonoscopy adherence into the cost-effectiveness analyses, greatly improving the accuracy of our results. Several model parameters were directly obtained from the Shanghai Screening Programme, including screening interval, sensitivity and specificity of each initial test, and colonoscopy adherence. The prevalence of CRC-related health states at baseline, transition probabilities, symptom-detected rates of CRC and mortality rates of CRC were also calibrated against the CRC incidence prior to the introduction of screening in Shanghai, China. These steps ensure the validity and applicability of our results in real-world screening practices.

There are several limitations to our study. First, due to the scarcity of data on serrated lesions in Chinese populations, related parameters were mainly obtained from the literature or based on assumptions, which may have biased our results. Nevertheless, these parameters were further calibrated against specific Chinese epidemiologic data, and sensitivity analyses showed no substantial changes in the results, proving the robustness of our results. Second, we considered direct medical costs only, which may have led to an underestimation of the total costs. However, sensitivity analyses demonstrated a very limited influence of costs on the cost-effectiveness evaluations. Finally, since the determination of an optimal strategy is greatly dependent on model parameters, our findings in the Chinese population may not be directly applicable to other populations, but they provide important insights into the cost-effectiveness analysis of CRC screening.

In conclusion, this model-based economic evaluation indicates that the currently used initial test in Shanghai is effective and cost-effective. Enhancing adherence to colonoscopy may further improve the cost-effectiveness of the programme, especially for reduction in incidence and detection of early-stage CRCs. Further investigations are warranted to adapt our microsimulation model to other populations by incorporating population-specific parameters derived from large-scale CRC screening practices.

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