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# Combining Colonoscopy With Fecal Immunochemical Test Can Improve Current Familial Colorectal Cancer Colonoscopy Surveillance: A Modelling Study

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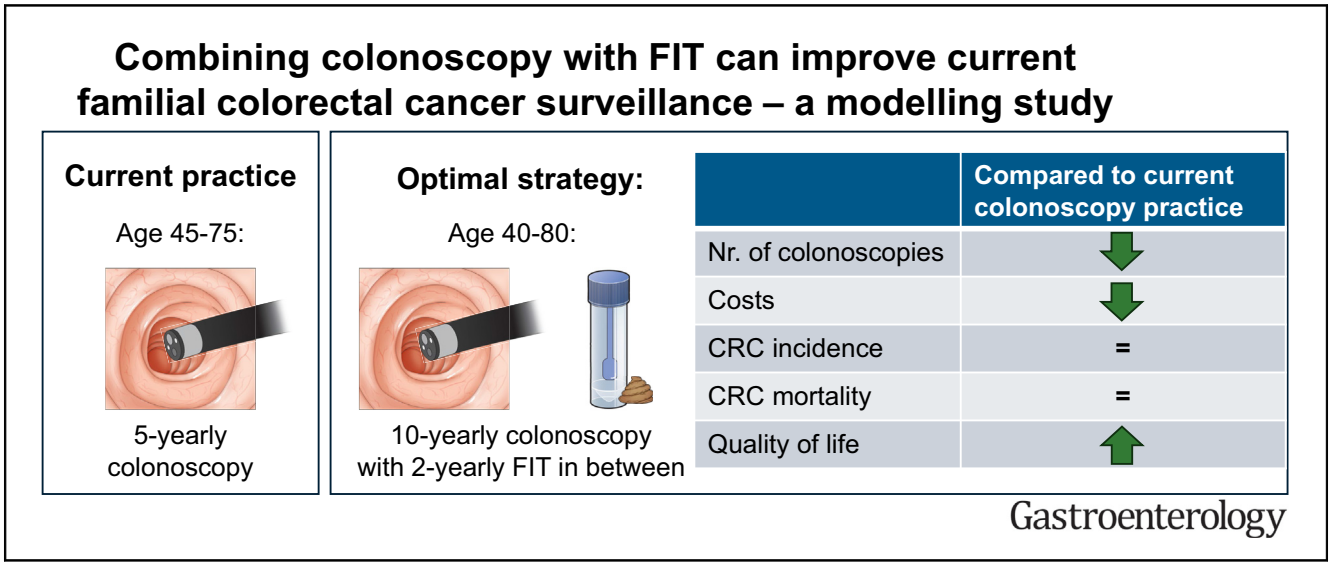


See editorial on page 10.

**BACKGROUND & AIMS:** The authors assessed whether familial colorectal cancer (FCRC) surveillance in individuals without hereditary CRC can be optimized **METHODS:** The Adenoma and Serrated Pathway to Colorectal Cancer (ASCCA)–FCRC model simulates CRC development in individuals with a family history of CRC at 2-fold and 4-fold increased CRC risk compared with the general population. The authors simulated a strategy without surveillance, the current Dutch guideline (5-yearly colonoscopy between ages 45 and 75 years), and the following 3 sets of alternative strategies: colonoscopy surveillance, surveillance combining colonoscopy and fecal immunochemical testing (FIT), and FIT-based surveillance. Each set included a range of strategies differing in age range and test interval. The optimal strategy was defined as the strategy with highest quality-adjusted life-years (QALYs) satisfying all of the following criteria: in the (near-)efficiency area of the cost-effectiveness frontier and compared with current surveillance; noninferior effectiveness; no substantial increase in colonoscopy burden; and not more expensive. **RESULTS:** The optimal strategy was 10-yearly colonoscopy with 2-yearly FIT between colonoscopies from ages 40 to 80 years for both 2-fold and 4-fold increased CRC risk. At 2-fold risk, this strategy prevented 0.8 more CRC deaths, gained 15.8 more QALYs at 731 fewer colonoscopies, and saved €98,000 over the lifetime of 1000 individuals compared with current surveillance. At 4-fold risk, figures were 2.1 more CRC deaths prevented, 37.0 more QALYs gained at 567 fewer colonoscopies, and €127,000 lower costs. Current surveillance was not (near-)efficient. **CONCLUSIONS:** FIT could play an important role in FCRC surveillance. Surveillance with 10-yearly colonoscopy and 2-yearly FIT between colonoscopies from ages 40 to 80 years

increased QALYs and reduced colonoscopy burden and costs compared with current FCRC surveillance.

*Keywords:* Family history; Optimization; Risk-Based.

**WHAT YOU NEED TO KNOW**

BACKGROUND AND CONTEXT

Current surveillance for individuals with a family history of colorectal cancer without an identified genetic origin may, at least for some subgroups, be too intensive.

NEW FINDINGS

A surveillance strategy in which colonoscopy and stool-based testing are alternated leads to more health gains and reduces colonoscopy burden and costs compared with current colonoscopy-based surveillance.

LIMITATIONS

Limited data were available on the level of colorectal cancer risk in individuals at increased familial risk and to inform the performance of the stool-based test in this population.

CLINICAL RESEARCH RELEVANCE

Fecal immunochemical test could play an important role in surveillance for individuals with a family history of colorectal cancer. Ten-yearly colonoscopy with 2-yearly fecal immunochemical test between ages 40 and 80 years was the optimal strategy. This strategy led to more health gains and reduced colonoscopy burden and costs compared with current surveillance, namely, 5-yearly colonoscopy from age 45 to 75 years. Current surveillance was not (near-)efficient in terms of cost-effectiveness.

BASIC RESEARCH RELEVANCE

The optimal strategy was determined using a multistep decision algorithm, which jointly considers multiple outcomes that are relevant to stakeholders in the field. The algorithm consisted of the following criteria: (near-) efficient in terms of incremental cost-effectiveness, noninferior effectiveness, no substantial increase in colonoscopy burden, and not more expensive.

Colorectal cancer (CRC) is a major health problem, as it is the second-leading cause of cancer deaths worldwide and accounts for 10% of all new cancer cases (approximately 1.9 million cases each year).[1] The vast majority of these CRCs appear to arise sporadically and/or are linked to lifestyle risk factors, but up to 30% have a familial component. Approximately 5% of all CRCs are due to an inherited cancer syndrome, such as familial adenomatous polyposis or Lynch syndrome. For the remaining 25% of CRCs with a familial component, no particular genetic origin has been identified as yet. These individuals are at an increased risk of CRC due to their family history (FH) and are the focus of this study.[2]

Multiple meta-analyses have evaluated the risk of developing CRC in individuals with an FH of CRC.[3–6] The relative risk compared with the general population varies across these studies. The relative CRC risk in individuals with at least 1 first-degree relative (FDR) diagnosed with CRC ranges between 1.8 and 2.2, and for those with at least 2 affected FDRs, the relative risk varies more widely, between 2.4 and 4.0. The confidence intervals surrounding the relative CRC risk estimates in individuals with an affected relative diagnosed with CRC at 50 years or older range between 1.6 and 3.0, and for those with an affected relative diagnosed before the age of 50 years, the intervals range between 1.8 and 6.8. One explanation for this variety could be heterogeneity in the study populations included. Therefore, it remains uncertain whether the risk of CRC differs significantly across FH groups based on number of FDRs diagnosed with CRC and/or the age of the FDR at diagnosis.

Individuals at increased CRC risk due to their FH are recommended surveillance colonoscopy to reduce that risk.[7] In the case of differing CRC risks among FH groups, there may be potential to personalize surveillance strategies to optimize efficiency and lower the surveillance burden. However, optimizing and personalizing surveillance recommendations is challenging when there is considerable uncertainty about the magnitude of CRC risk, which is reflected in the differences among surveillance recommendations internationally.[7,8]

Due to the invasiveness of a colonoscopy, there is a growing interest in exploring less invasive strategies for surveillance. Studies have suggested that among individuals with an increased risk due to their FH, the CRC risk is lower for those with no lesions or only low-risk findings, for example, nonadvanced adenoma or nonadvanced serrated lesions (<10 mm without dysplasia) detected at colonoscopy.[9,10] Therefore, it is worthwhile to investigate whether the interval between surveillance colonoscopies can be extended for these individuals. Moreover, it would also be interesting to explore the potential of fecal immunochemical testing (FIT) in guiding the timing of colonoscopy, or even as a potential substitute for colonoscopy.[11]

Decision-analytic modelling can provide useful guidance for optimizing surveillance in individuals with an FH of CRC without hereditary CRC. In particular, modelling allows for explicitly studying the impact of uncertainty with regard to CRC risk on optimal surveillance recommendations. With this study, we assessed whether surveillance in individuals with an FH of CRC can be optimized in terms of cost-effectiveness, effectiveness, colonoscopy burden, and costs by tailoring surveillance to the level of CRC risk and by using stool-based testing to guide the timing of colonoscopies.

***Abbreviations used in this paper:*** **AA, advanced adenoma; ASCCA, Adenoma and Serrated Pathway to Colorectal Cancer; CRC, colorectal cancer; FACTS, Familial Colorectal Cancer Surveillance study; FCRC, familial colorectal cancer; FDR, first-degree relative; FH, family history; FIT, fecal immunochemical test; QALY, quality-adjusted life-year.**

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## Materials and Methods

### Adenoma and Serrated Pathway to Colorectal Cancer–Familial Colorectal Cancer Model

To evaluate alternative surveillance strategies in individuals with an FH of CRC without hereditary CRC, the Adenoma and Serrated Pathway to Colorectal Cancer (ASCCA) model was used. The ASCCA model simulates the natural history of CRC and incorporates the conventional adenoma-to-carcinoma pathway and the serrated pathway in CRC development. It reproduces the Dutch age- and sex-specific colorectal lesion prevalence, as well as age- and sex-specific CRC incidence and CRC-related mortality rates in the general population in the absence of screening.[12] A flexible screening and surveillance component is included in the model and the model is programmed in C++11.

To evaluate surveillance in a population at increased CRC risk due to their FH, adaptation of the risk to develop CRC in the ASCCA model was required. Given that the exact magnitude of CRC risk and the difference in risk between FH groups are not well known,[3–6] we adapted the ASCCA model for 2 levels of CRC risk, that is, for a scenario in which CRC risk in individuals with an FH of CRC is increased by 2-fold and for a scenario in which the risk is 4-fold compared with the general population. Two different mechanisms driving this increased risk were evaluated, namely, that the increased risk is due to an increased polyp incidence or due to an increased progression of adenomas to CRC (Supplementary Figure 1). Subsequently, we validated the adapted ASCCA-FCRC model by replicating the Familial Colorectal Cancer Surveillance (FACTS) study under both mechanisms.[9] The FACTS study included individuals who had 1 FDR diagnosed with CRC before 50 years of age or 2 FDRs diagnosed with CRC at any age. Participants were randomized to colonoscopy surveillance at either a 3-year interval or a 6-year interval. The model predictions were closest to the adenoma and AA detection rates, as observed in the FACTS study, under the assumption that increased risk is due to an increased polyp incidence (Supplementary Figure 2). Limited evidence also suggested increased polyp incidence to be the main driver of increased CRC risk in individuals with an FH.[13] Therefore, the main analysis was performed assuming that the increased CRC risk is due to increased lesion incidence rates, and the assumption of increased progression was considered in a sensitivity analysis. An overview of all input parameters is provided in Supplementary Table 1.

### Surveillance Strategies

We first set up the ASCCA-FCRC model to simulate a strategy without surveillance. That is, individuals do not undergo colonoscopy or FIT. Subsequently, we simulated current surveillance consisting of 5-yearly colonoscopy between ages 45 and 75 years.[8] Note that this surveillance scheme is recommended in the Netherlands for individuals with 2 or more FDRs diagnosed with CRC between ages 50 and 70 years, individuals with 1 FDR diagnosed with CRC between ages 50 and 70 years and a second-degree relative diagnosed with CRC before age 70 years, and individuals with an FDR diagnosed with a CRC before age 50 years, after exclusion of hereditary CRC.[8]

Then, the following 3 alternative sets of strategies were simulated: 1) colonoscopy-based surveillance, 2) surveillance in which colonoscopy and FIT are alternated, and 3) FIT-based surveillance. For each set, we simulated a range of strategies, differing in start and stop ages and test intervals. An overview of all evaluated strategies is provided in Table 1. In all strategies, we assumed that the 2022 Dutch post-polypectomy guideline would apply to individuals classified as high risk (Table 1).[14] Note that this means that only FIT-negative individuals and those who were classified as low risk during an FH surveillance colonoscopy undergo the proposed FH surveillance strategies. As it can therefore be expected that CRC risk decreases over time for those who remain under FH surveillance, strategies in which the intensity of surveillance was reduced over time were also included. For example, we evaluated colonoscopy-based surveillance strategies in which individuals first undergo 2 or 4 colonoscopies with an interval of 3 or 5 years, followed by colonoscopies with an extended interval of 10 years or followed by FIT. For the strategies in which colonoscopy was followed by FIT, the added benefit of having an exit colonoscopy at the stop age was also evaluated. We assumed perfect adherence (100%) to all tests, namely, colonoscopy, FIT, and follow-up colonoscopy after a positive FIT, thereby predicting the benefits, burden, and costs of surveillance among participating individuals. A sensitivity analysis was performed assuming realistic adherence. More details about this sensitivity analysis can be found below. FIT was evaluated at a threshold of 15 $\mu$g/g (Supplementary Table 2).

### Outcomes

Outcomes of each strategy included CRC cases and CRC-related deaths, the number of colonoscopies performed, quality-adjusted life-years (QALYs), and costs. The number of colonoscopies is the total number of colonoscopies performed, thus both colonoscopies related to FCRC surveillance and to post-polypectomy surveillance. Costs were determined from a health care payer perspective and were converted to 2022 euros based on the Consumer Price Index and purchasing power parity (Supplementary Table 1).[15,16] Costs and QALYs were discounted using a standard annual rate of 3%.[17] All outcomes were calculated for the lifetime of a cohort of 1000 individuals starting at age 40 years, which is the youngest age that individuals start with surveillance in the evaluated strategies.

### Cost-Effectiveness Analysis

The QALYs gained and the euros spent for all strategies were plotted in a cost-effectiveness plane. In this plane, the efficiency frontier was identified, which is the line connecting the efficient strategies, meaning strategies providing the largest incremental gain in QALYs per euro spent. Strategies were considered to be near-efficient when the predicted QALYs gained were within 2% of the efficiency frontier (Supplementary Figure 3).

### Optimal Surveillance Strategy

We used 4 criteria concerning cost-effectiveness, costs, effectiveness, and burden of surveillance to select strategies that we deemed suitable for recommendation. Firstly, strategies needed to be near-efficient or efficient in terms of cost-effectiveness. Secondly, only strategies with noninferior effectiveness compared with current surveillance were considered a

**Table 1.** Overview of Evaluated Surveillance Strategies for Individuals With a Family History of Colorectal Cancer

| Test | Interval |
|---|---|
| Colonoscopy | 5-yearly<br>3-yearly[a]<br>10-yearly<br>2 rounds of 3-yearly followed by 10-yearly<br>4 rounds of 3-yearly followed by 10-yearly<br>2 rounds of 5-yearly followed by 10-yearly<br>4 rounds of 5-yearly followed by 10-yearly |
| Colonoscopy and FIT[b] | 2 rounds of 3-yearly colonoscopy followed by yearly FIT<br>2 rounds of 3-yearly colonoscopy followed by 2-yearly FIT<br>4 rounds of 3-yearly colonoscopy followed by yearly FIT<br>4 rounds of 3-yearly colonoscopy followed by 2-yearly FIT<br>2 rounds of 5-yearly colonoscopy followed by yearly FIT<br>2 rounds of 5-yearly colonoscopy followed by 2-yearly FIT<br>4 rounds of 5-yearly colonoscopy followed by yearly FIT<br>4 rounds of 5-yearly colonoscopy followed by 2-yearly FIT<br>4 rounds of 5-yearly colonoscopy followed by yearly FIT and exit colonoscopy at stop age<br>4 rounds of 5-yearly colonoscopy followed by 2-yearly FIT and exit colonoscopy at stop age<br>10-yearly colonoscopy with yearly FIT<br>10-yearly colonoscopy with 2-yearly FIT |
| FIT[b] | Yearly<br>2-yearly |

NOTE. All strategies were evaluated between the following start and stop ages: 40 and 75 years, 40 and 80 years, 45 and 75 years, and 45 and 80 years. For all strategies, we assumed that the 2022 Dutch post-polypectomy guideline would apply to individuals classified as high risk.[14] An individual was classified as high risk when an adenoma ≥10 mm and/or with high-grade dysplasia, a serrated polyp ≥10 mm and/or with dysplasia, or at least 5 low-risk adenomas were detected during a surveillance colonoscopy or during a follow-up colonoscopy after a positive FIT result. Once individuals enter post-polypectomy surveillance, they are assumed to undergo a colonoscopy every 3 years, with the interval being extended to 5 or 10 years after 1 or 2 subsequent colonoscopies without high-risk findings. According to that guideline, post-polypectomy surveillance was assumed to end at age 80 years.

[a]The post-polypectomy surveillance guideline does not apply in this strategy, as the evaluated surveillance strategy is more intensive than the post-polypectomy guideline.

[b]FIT at a threshold of 15 μg/g.

realistic alternative. Noninferior effectiveness was defined as preventing at least 95% of the CRC cases and 95% of the CRC deaths that would be prevented by current Dutch surveillance and gaining at least 95% of the QALYs gained by current surveillance compared with no surveillance. These criteria were based on discussions with experts. Thirdly, strategies that resulted in a substantial increase in colonoscopy burden (>10% more colonoscopies than current surveillance) were considered undesirable and were thus excluded. Fourthly, strategies that were predicted to be more expensive than current surveillance were excluded. Among those strategies satisfying the above 4 criteria, the strategy with the highest QALYs was selected as the optimal strategy. The optimal strategy was identified separately for those at a 2-fold and a 4-fold CRC risk.

Instead of determining the optimal strategy for both risk groups separately, it is also possible to optimize surveillance by determining the optimal combination strategy. For the former analysis, each of the 4 criteria for determining optimality needs to be satisfied for each of the risk groups separately, and for the latter, these criteria only need to be satisfied marginally, that is, for both risk groups jointly. This means that the optimal combination strategy may, for example, contain more intensive use of surveillance colonoscopies and financial resources in the high-risk group than would have been considered optimal for that group, at the cost of colonoscopies and financial resources in the low-risk group because relatively more QALYs and a higher reduction in CRC death are achieved in the former group. To test this joint optimization, we performed an additional analysis in which we identified the optimal combination of strategies for the entire FH population consisting of individuals at both low risk (2-fold) and high risk (4-fold). To do so, all possible combinations of strategies for the 2 risk groups were obtained. Given that the distribution of individuals at low or high risk within the FH population is unknown, we considered 3 hypothetical scenarios with varying distributions, namely, a distribution of 25% low risk and 75% high risk, 50% low risk and 50% high risk, and 75% low risk and 25% high risk. For each of these 3 distribution scenarios, we identified the optimal strategy combination by applying the same 4 criteria as in the main analysis on the outcomes of the 2 risk groups combined.

### Sensitivity Analyses

The robustness of our results was assessed in sensitivity analyses. We conducted 4 sensitivity analyses assuming imperfect participation. In 2 of these analyses, we assumed that participation rates for colonoscopy and FIT were equal, with each individual having a 50% (analysis 1) and a 70% (analysis 2) random probability of participating in each round.[18–20] Because FIT is less invasive than colonoscopy, it can be expected that participation for FIT is higher compared with participation for colonoscopy. Therefore, we performed 2 additional sensitivity analyses assuming higher participation for FIT than for colonoscopy: 1 with 50% participation for FIT and 30% for colonoscopy, and another with 85% participation for FIT and 70% for colonoscopy. In all analyses assuming imperfect participation, compliance with follow-up colonoscopy after a positive FIT was set at 92% based on the participation observed in the Dutch CRC screening program.[21] To assess the impact of lower colonoscopy quality, a sensitivity analysis was conducted assuming a 10% higher miss rate of colonoscopy for all precursor lesions. In addition, to evaluate the impact of lower FIT sensitivity, we repeated all analyses with a 10% lower per-lesion FIT sensitivity for large adenomas (Supplementary Table 2). In addition, we repeated the analysis with an FIT threshold of 10 $\mu$g/g instead of 15 $\mu$g/g. Furthermore, a sensitivity analysis was conducted assuming FIT costs of €15 instead of €26. Lastly, a sensitivity analysis was conducted assuming that CRC risk was raised due to an increased progression of adenomas to CRC. An overview of the model parameters in the sensitivity analyses can be found in Supplementary Table 3.



## Results

### Colorectal Cancer Cases, Deaths, and Number of Colonoscopies

In the absence of surveillance, the ASCCA-FCRC model predicted a total of 124 CRC cases and 52 CRC deaths in the lifetime of 1000 individuals when assuming 2-fold increased CRC risk compared with the general population. When assuming 4-fold increased CRC risk, the number of CRC cases and deaths was 214 and 93, respectively (data not shown). Surveillance was predicted to prevent a considerable number of CRC cases (n = 82–118 [66.6%–95.7%]) for 2-fold and (n = 144–203 [67.3%–94.7%]) for 4-fold CRC risk, and a considerable number of CRC deaths (n = 42–51 [81.2%–97.6%]) for 2-fold and (n = 76–90 [81.7%–97.0%]) for 4-fold CRC risk (Supplementary Table 4).

In the lifetime of 1000 individuals, current surveillance with 5-yearly colonoscopy was predicted to prevent 111 CRC cases and 49 CRC deaths, while requiring 6393 colonoscopies when assuming 2-fold increased CRC risk, and 188 CRC cases and 86 CRC deaths requiring 6544 colonoscopies when assuming 4-fold increased risk.

### Cost-Effectiveness Analysis

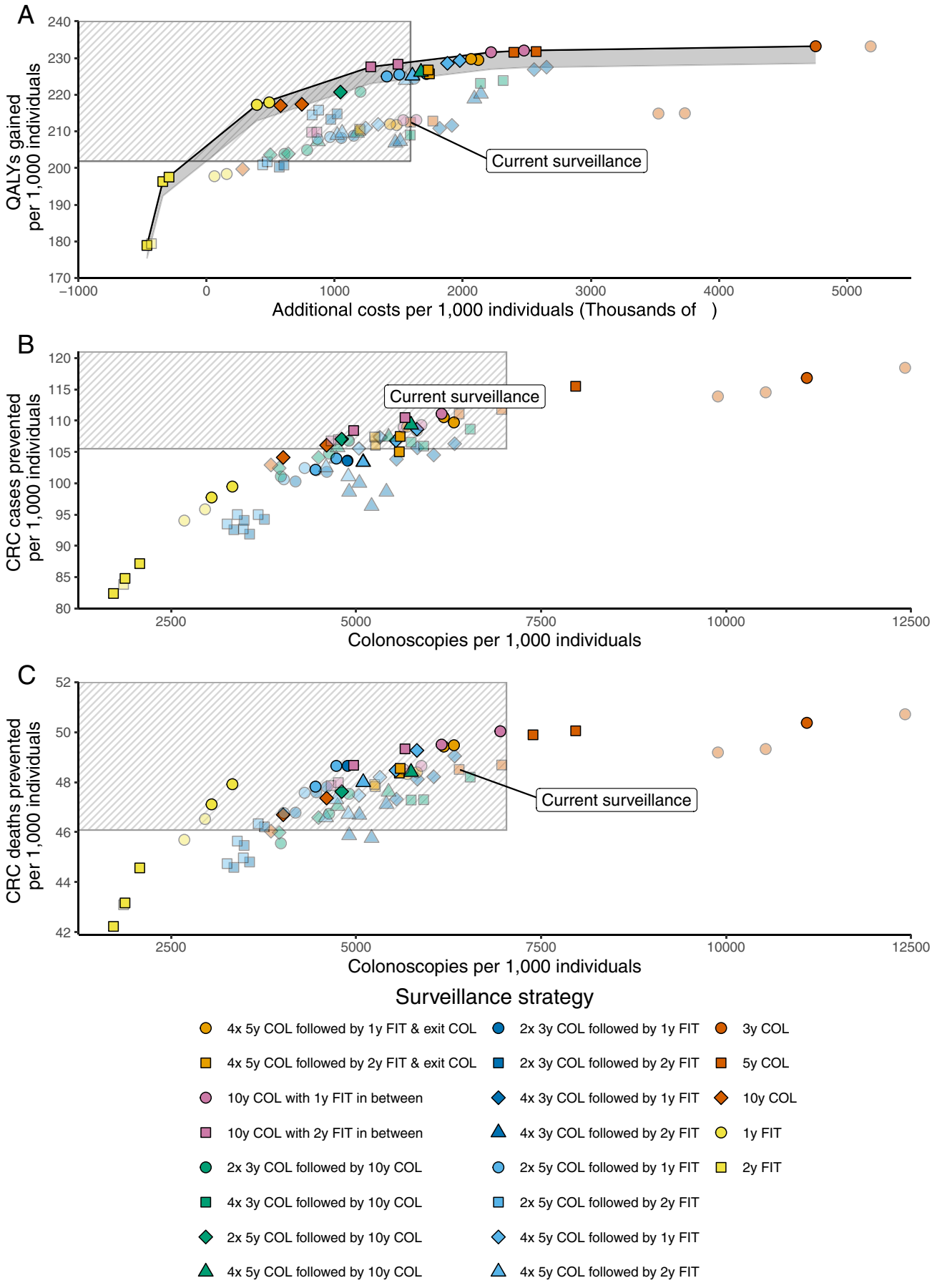
Figures 1*A* and 2*A* depict the discounted QALYs and costs of all strategies assuming 100% participation, as well as the efficiency frontier with the area of near efficiency, under a 2-fold and 4-fold increased CRC risk, respectively, compared with the general population. There was a range of (near-)efficient strategies, including colonoscopy-based strategies, strategies in which colonoscopy and FIT were alternated, and FIT-based strategies (Table 2). The starting age of almost all (near-)efficient strategies was 40 years, except for the first strategy on the efficiency frontier, namely, 2-yearly FIT from age 45 to 75 years. Current surveillance was not a (near-)efficient strategy.

### Optimal Surveillance Strategy

Among the (near-)efficient strategies under the assumption of 2-fold increased CRC risk, there were 4 strategies, namely, 10-yearly colonoscopy from age 40 to 80 years, 2 rounds of 5-yearly colonoscopy followed by 10-yearly colonoscopy from age 40 to 75 years, and 10-yearly colonoscopy with 2-yearly FIT between ages 40 to 75 years, and between ages 40 to 80 years, that satisfied the 4 criteria concerning cost-effectiveness, effectiveness, colonoscopy burden, and costs (Figure 1 and Table 2). Of those 4, 10-yearly colonoscopy with 2-yearly FIT in between ages 40 and 80 years was the optimal strategy with the highest number of QALYs (228 QALYs gained per 1000 individuals compared with no surveillance). Relative to current surveillance, this strategy resulted in a similar reduction in CRC cases and deaths and 7.4% more QALYs gained, at 11.4% fewer colonoscopies performed and €98,000 lower costs per 1000 individuals.

For individuals at 4-fold risk, there were 5 strategies that satisfied the 4 criteria, namely, the same 4 strategies as for 2-fold risk plus the strategy of 2 rounds of 5-yearly colonoscopy, followed by yearly FIT from age 40 to 80 years (Figure 2 and Table 2). Of these 5 strategies, 10-yearly colonoscopy with 2-yearly FIT in between ages 40 and 80 years was the optimal strategy with the highest number of QALYs, the same optimal strategy as for individuals at 2-fold risk. This strategy resulted in a similar reduction in CRC cases and deaths and 9.1% more QALYs gained compared with current surveillance, at 8.7% fewer colonoscopies performed and €127,000 lower costs per 1000 individuals. The combination of optimal strategies was thus 10-yearly colonoscopy with 2-yearly FIT between ages 40 and 80 years for both risk groups (2-fold and 4-fold CRC risk).

In the additional analysis, where it was possible to shift financial resources and colonoscopies between the low- and high-risk groups (2-fold and 4-fold, respectively) by identifying the optimal combination strategy for the entire FH population, results were similar (Supplementary Table 5). In 2 of the 3 scenarios with varying distribution of individuals at low and high risk within the FH population, the identified combination strategy was 10-yearly colonoscopy with either yearly or 2-yearly FIT between colonoscopies for both risk groups, which is the same as the strategies identified per risk group, although the interval of FIT and the start and stop ages varied. In the third distribution scenario, the combination strategy consisted of 10-yearly colonoscopy with 2-yearly FIT between colonoscopies for the low-risk group and 4 rounds of 5-yearly colonoscopy followed by yearly FIT for the high-risk group.


A
QALYs gained per 1,000 individuals
Current surveillance
Additional costs per 1,000 individuals (Thousands of )
B
CRC cases prevented per 1,000 individuals
Current surveillance
Colonoscopies per 1,000 individuals
C
CRC deaths prevented per 1,000 individuals
Current surveillance
Colonoscopies per 1,000 individuals
Surveillance strategy
4x 5y COL followed by 1y FIT & exit COL
4x 5y COL followed by 2y FIT & exit COL
10y COL with 1y FIT in between
10y COL with 2y FIT in between
2x 3y COL followed by 10y COL
4x 3y COL followed by 10y COL
2x 5y COL followed by 10y COL
4x 5y COL followed by 10y COL
2x 3y COL followed by 1y FIT
2x 3y COL followed by 2y FIT
4x 3y COL followed by 1y FIT
4x 3y COL followed by 2y FIT
2x 5y COL followed by 1y FIT
2x 5y COL followed by 2y FIT
4x 5y COL followed by 1y FIT
4x 5y COL followed by 2y FIT
3y COL
5y COL
10y COL
1y FIT
2y FIT

### Sensitivity Analysis

An overview of the optimal strategies across all sensitivity analyses can be found in Table 3. For the 2-fold risk group, the optimal strategy in 6 of the 9 sensitivity analyses was 10-yearly colonoscopy with 2-yearly FIT between ages 40 and 80 years, consistent with the main analysis (Supplementary Figures 6, 8–12, and Supplementary Tables 8, 10–14). In the sensitivity analysis assuming 85% participation for FIT and 70% participation for colonoscopy, the optimal strategy was similar, but with a stop age of 75 years (Supplementary Figure 7 and Supplementary Table 9). When assuming 30% participation for colonoscopy and 50% participation for FIT, yearly FIT from age 40 to 80 years was identified as optimal (Supplementary Figure 4 and Supplementary Table 6). In the analysis assuming 50% participation for both colonoscopy and FIT, no optimal strategy was identified (Supplementary Figure 5 and Supplementary Table 7). However, yearly FIT from age 40 to 80 years satisfied 3 of the 4 criteria, as 93.3% of the CRC cases were prevented instead of the required 95%. For the 4-fold risk group, the optimal strategy was consistent with the main analysis in 5 of the 9 sensitivity analyses (Supplementary Figures 16–20 and Supplementary Tables 9–13). In the 2 sensitivity analyses assuming 70% participation for colonoscopy and FIT, and assuming that CRC risk was increased due to increased progression, 10-yearly colonoscopy with 2-yearly FIT between ages 40 and 80 years satisfied all 4 criteria, but an alternative strategy, consisting of 2 rounds of 3-yearly or 5-yearly colonoscopy followed by yearly FIT, was predicted to gain slightly more QALYs and was thus was identified as optimal (Supplementary Figures 15 and 21 and Supplementary Tables 8 and 14). In the 2 remaining sensitivity analyses, assuming 50% participation for both colonoscopy and FIT, and assuming 30% participation for colonoscopy and 50% for FIT, the optimal strategy was yearly FIT from age 40 to 80 years (Supplementary Figures 13 and 14 and Supplementary Tables 6 and 7).

## Discussion

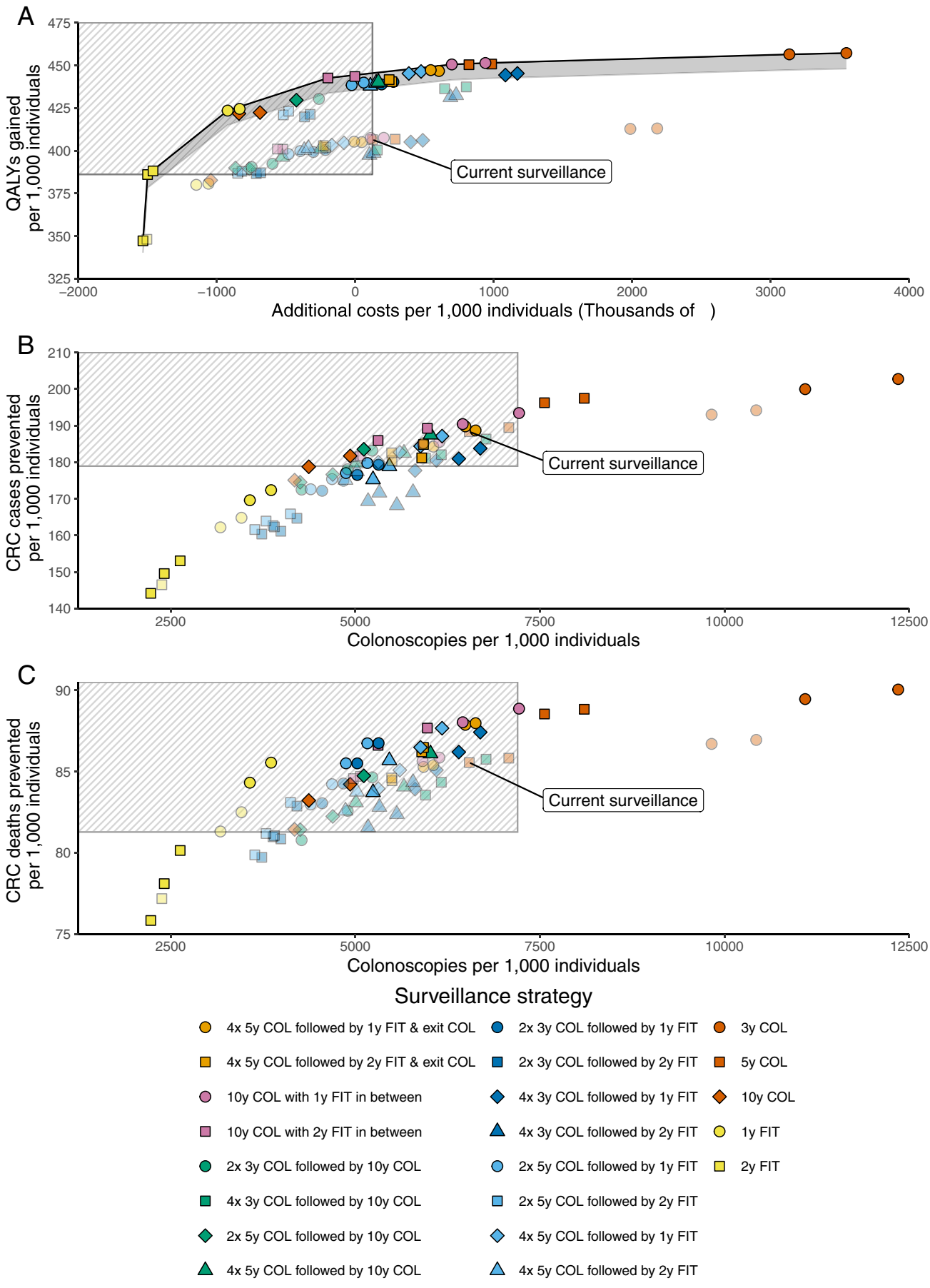
Our modelling study aimed to optimize surveillance in individuals with an FH of CRC (and exclusion of a known hereditary CRC syndrome or polyposis) in terms of cost-effectiveness, but also in terms of noninferior effectiveness, no substantial increase in colonoscopy burden and no increase in costs compared with current surveillance. We found that FIT could play a crucial role in surveillance within this population, as multiple strategies that include FIT in a de-intensified colonoscopy schedule led to more efficient use of resources without compromising effectiveness compared with current colonoscopy surveillance. The current Dutch surveillance strategy of 5-yearly colonoscopy from age 45 to 75 years was not (near-)efficient in terms of cost-effectiveness for levels of CRC risk broadly consistent with the literature.[3–6] The optimal strategy in our study was 10-yearly colonoscopy with 2-yearly FIT between ages 40 and 80 years. This strategy gained QALYs, prevented more CRC deaths, and reduced colonoscopy burden and costs compared with current Dutch colonoscopy surveillance. Optimizing surveillance for the high and low FCRC risk group jointly, by allowing financial resources and colonoscopies to flow from one risk group to the other, also resulted in optimal strategies in which colonoscopy and FIT are combined, similar to the main analysis.

To our knowledge, this is the first study that evaluated strategies for individuals with an FH of CRC in which colonoscopy and FIT are alternated. By contrast, colonoscopy-based surveillance strategies for individuals with an FH of CRC were evaluated by several modelling studies.[22,23] In the modelling study by Naber et al,[22] the cost-effectiveness of surveillance strategies was assessed for different levels of CRC risk. They found that, from the viewpoint of cost-effectiveness, the colonoscopy interval could be extended gradually from 3 years at age 35 years to 7 years at age 70 years for those with persistent negative results for individuals with 2 affected FDRs (relative risk between 1.7 and 8.7, depending on the age of the person at risk of CRC). Had we restricted our analysis to colonoscopy-based surveillance strategies, a somewhat similar strategy would have been considered optimal, namely, switching from 5-yearly colonoscopy to 10-yearly colonoscopy after 2 negative colonoscopies.

Another modelling study, by Wilschut et al,[23] assigned different CRC risks to different categories of FH, depending on the number of FDRs diagnosed with CRC and the age at which the FDR was diagnosed. They found that surveillance strategies with a higher total number of screens resulted in lower incremental cost-effectiveness ratios for FH categories with higher risk compared with those with lower risk. We also found that more intensive surveillance strategies are more cost-effective in individuals with higher CRC risk compared with lower CRC risk because all strategies were found to be cheaper and resulted in greater QALY gains in the 4-fold risk group compared with a 2-fold group. Nevertheless, the more intensive surveillance strategies were not selected as optimal for the 4-fold group in our study, as they exceeded the costs of current surveillance. This criterion was not considered in the study by Wilschut et al.

Interest in less invasive surveillance is increasing, leading to evaluations of FIT-based surveillance strategies

**Figure 1.** Predicted outcomes of surveillance strategies for individuals at 2-fold CRC risk. *Panel A* shows the QALYs gained vs costs spent and *panels B* and *C* show the CRC cases and CRC deaths prevented, respectively, vs the colonoscopy burden. Results are presented for a cohort of 1000 individuals compared with no surveillance and assuming 100% participation to colonoscopy and FIT. In *panel A*, the *black line* represents the efficiency frontier and the *gray band* represents what is (near)-efficient. Strategies in the *gray striped rectangle* meet the criteria regarding QALYs gained and costs. In *panels B* and *C*, strategies in the *gray striped rectangle* meet the criteria for CRC cases and deaths prevented and colonoscopy burden. Strategies that are partially transparent are not (near)-efficient. COL, colonoscopy.


A
QALYs gained per 1,000 individuals
Additional costs per 1,000 individuals (Thousands of )
Current surveillance
B
CRC cases prevented per 1,000 individuals
Colonoscopies per 1,000 individuals
Current surveillance
C
CRC deaths prevented per 1,000 individuals
Colonoscopies per 1,000 individuals
Current surveillance
Surveillance strategy
4x 5y COL followed by 1y FIT & exit COL
4x 5y COL followed by 2y FIT & exit COL
10y COL with 1y FIT in between
10y COL with 2y FIT in between
2x 3y COL followed by 10y COL
4x 3y COL followed by 10y COL
2x 5y COL followed by 10y COL
4x 5y COL followed by 10y COL
2x 3y COL followed by 1y FIT
2x 3y COL followed by 2y FIT
4x 3y COL followed by 1y FIT
4x 3y COL followed by 2y FIT
2x 5y COL followed by 1y FIT
2x 5y COL followed by 2y FIT
4x 5y COL followed by 1y FIT
4x 5y COL followed by 2y FIT
3y COL
5y COL
10y COL
1y FIT
2y FIT

instead of colonoscopy-based strategies. The MOCCAS (MOlecular stool testing for Colorectal CAncer Surveillance) study, a cross-sectional cohort study evaluating the performance of stool tests in a surveillance setting, predicts that stool-based surveillance can be as effective as post-polypectomy colonoscopy surveillance, while reducing the number of colonoscopies by up to 41% without increasing health care costs.[24,25] In a previous study by Quintero et al,[26] individuals with a first-degree FH of CRC were randomly assigned to either colonoscopy after 3 years or yearly FIT for 3 years. The results indicated a lower cumulative advanced adenoma (AA) detection rate of yearly FIT compared with colonoscopy, 3.6% and 5.0%, respectively, although the differences in detection rates did not exceed their predefined equivalence boundary of 3%. These results may suggest a lower efficacy of yearly FIT in detecting AA compared with 3-yearly colonoscopy, and these missed AAs could progress to CRC. Our findings also support this, as we found that yearly FIT was less effective than 3-yearly colonoscopy in terms of number of prevented CRC cases in this population. Nevertheless, strategies that combine FIT with colonoscopy may enhance detection of advanced neoplasia. This was observed in a cohort study by Lane et al[27] in individuals with past neoplasia or FH with CRC, where yearly FIT combined with 5-yearly colonoscopy was found to detect advanced neoplasia sooner than 5-yearly colonoscopy alone. Our study, which takes a long-term perspective, even suggests that the recommended interval of colonoscopy can be as long as 10 years when colonoscopy is combined with FIT.

There is 1 other modelling study by Benamouzig et al[28] that evaluated surveillance including both FIT- and colonoscopy-based strategies for individuals with FH of CRC starting at age 45 until age 75 years. Our findings are in line with the results of that study. In the analysis in which they assumed equal participation of 30% for FIT and colonoscopy, 2-yearly FIT at a threshold of 15 $\mu$g/g was not found to be as effective in terms of QALYs as 5-yearly colonoscopy, which was also found in our study when assuming equal participation of 50%. They also performed a sensitivity analysis assuming higher participation for FIT (45%) than colonoscopy (30%). Under that assumption, 2-yearly FIT was found to be more effective than 5-yearly colonoscopy. In our sensitivity analysis assuming 50% participation for FIT and 30% for colonoscopy, 2-yearly FIT was also predicted to gain more QALYs than 5-yearly colonoscopy.

Before contemplating a change in surveillance guidelines, patients' attitudes toward such a change should be included. A study by Dix et al[29] found that most individuals under colonoscopy surveillance would be uncomfortable with colonoscopy-based surveillance being replaced by FIT-based surveillance. In our optimal strategy, colonoscopy-based surveillance is combined with FIT. The attitude toward such a strategy was not evaluated by Dix et al. In this optimal strategy, individuals will still get regular colonoscopies combined with FIT, although the interval between colonoscopies is extended. When clearly communicated, this may increase acceptance of such a strategy. However, in settings where colonoscopy serves as the standard test not only for surveillance in high-risk individuals, but even for screening in the general population, FIT, a test with lower sensitivity than colonoscopy, may not be considered acceptable for surveillance. Moreover, logistical challenges associated with introducing stool-based testing in surveillance should also be taken into account. For example, programmatic FIT testing in the Netherlands is currently only performed within the framework of the Dutch national screening program. Surveillance for individuals with an FH of CRC operates independently of this program. Thus, if FIT testing is to be added to FCRC surveillance, it has yet to be established who will be responsible for delivering the FITs (eg, the hospital or general practitioners), and where the analysis of FIT samples with take place.

With our study, we aimed to evaluate whether the optimal surveillance strategy would differ for different levels of CRC risk (2-fold and 4-fold). A 4-fold increased CRC risk may appear relatively high for individuals with an FH without a hereditary cancer syndrome, approaching the upper limit of reported risks in literature.[3–6] Nonetheless, given the substantial uncertainty surrounding these risk estimates, we deliberately assessed a more extreme scenario. Furthermore, the outcomes from the 2-fold and 4-fold groups can be interpolated to, for instance, a 3-fold increased CRC risk. In addition, it should be noted that this study was conducted from a Dutch perspective. However, by explicitly simulating 2 different CRC risk groups, results could be generalized to other countries with higher baseline CRC risk than the Netherlands, such as those with greater racial or ethnic diversity. For these countries, the results of the 4-fold group are particularly relevant.

We showed that the optimal strategy is robust for different levels of CRC risk, as the same strategy was found to be optimal for both levels of CRC risk. Even when shifting resources between the risk groups was possible, results were very similar to those obtained from combining the optimal strategies that were found for the risk groups separately. Therefore, our results indicate that it is preferable to not recommend personalized surveillance across individuals in FH



**Figure 2.** Predicted outcomes of surveillance strategies for individuals at 4-fold CRC risk. *Panel A* shows the QALYs gained vs costs spent and *panels B* and *C* show the CRC cases and CRC deaths prevented, respectively, vs the colonoscopy burden. Results are presented for a cohort of 1000 individuals compared with no surveillance and assuming 100% participation to colonoscopy and FIT. In *panel A*, the *black line* represents the efficiency frontier and the *gray band* represents what is (near)-efficient. Strategies in the *gray striped rectangle* meet the criteria regarding QALYs gained and costs. In *panels B* and *C*, strategies in the *gray striped rectangle* meet the criteria for CRC cases and deaths prevented and colonoscopy burden. Strategies that are partially transparent are not (near)-efficient. COL, colonoscopy.

**Table 2.** Predicted Outcomes of (Near-)Efficient Surveillance Strategies Assuming 100% Participation to Colonoscopy and Fecal Immunochemical Test

| | | Outcomes per 1000 individuals compared with no surveillance | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Prevented, n | | | | |
| Test and interval | Start–stop age, *y* | QALYs gained, n | CRC cases | CRC deaths | COLs, n | Costs, € | Optimal strategy[a] |
| 2-Fold CRC risk compared with the general population | | | | | | | |
| 5-y COL (current surveillance)[b] | 45–75 | 212 | 111 | 49 | 6393 | 1,592,300 | — |
| 2-y FIT | 45–75 | 179 | 82 | 42 | 1723[c] | –465,888[d] | — |
| 2-y FIT | 40–75 | 196 | 85 | 43 | 1879[c] | –342,099[d] | — |
| 2-y FIT | 40–80 | 198 | 87 | 45 | 2078[c] | –293,105[d] | — |
| 10-y COL | 40–75 | 217[e] | 104 | 47[e] | 4016[c] | 577,797[d] | — |
| 1-y FIT | 40–75 | 217[e] | 98 | 47[e] | 3049[c] | 392,464[d] | — |
| 10-y COL | 40–80 | 217[e] | 106[e] | 47[e] | 4603[c] | 743,855[d] | — |
| 1-y FIT | 40–80 | 218[e] | 99 | 48[e] | 3329[c] | 488,978[d] | — |
| 2× 5-y COL followed by 10-y COL | 40–75 | 221[e] | 107[e] | 48[e] | 4807[c] | 1,045,166[d] | — |
| 2× 5-y COL followed by 1-y FIT | 40–75 | 225[e] | 102 | 48[e] | 4453[c] | 1,406,999[d] | — |
| 4× 5-y COL followed by 2-y FIT | 40–80 | 225[e] | 103 | 48[e] | 5097[c] | 1,606,820 | — |
| 2× 5-y COL followed by 1-y FIT | 40–80 | 225[e] | 104 | 49[e] | 4734[c] | 1,503,958[d] | — |
| 2× 3-y COL followed by 1-y FIT | 40–80 | 226[e] | 104 | 49[e] | 4887[c] | 1,716,464 | — |
| 4× 5-y COL followed by 2-y FIT and exit COL | 40–80 | 226[e] | 105 | 48[e] | 5585[c] | 1,739,899 | — |
| 4× 5-y COL followed by 10-y COL | 40–75 | 226[e] | 109[e] | 48[e] | 5743[c] | 1,673,866 | — |
| 4× 5-y COL followed by 2-y FIT and exit COL | 40–75 | 227[e] | 107[e] | 49[e] | 5596[c] | 1,730,483 | — |
| 10-y COL with 2y FIT | 40–75 | 228[e] | 108[e] | 49[e] | 4968[c] | 1,282,007[d] | — |
| 10-y COL with 2y FIT | 40–80 | 228[e] | 110[e] | 49[e] | 5662[c] | 1,494,329[d] | Yes |
| 4× 5-y COL followed by 1-y FIT | 40–75 | 229[e] | 107[e] | 48[e] | 5540[c] | 1,880,369 | — |
| 4× 5-y COL followed by 1-y FIT | 40–80 | 229[e] | 109[e] | 49[e] | 5823[c] | 1,977,357 | — |
| 4× 5-y COL followed by 1-y FIT and exit COL | 40–80 | 229[e] | 110[e] | 49[e] | 6323[c] | 2,121,321 | — |
| 4× 5-y COL followed by 1-y FIT and exit COL | 40–75 | 230[e] | 111[e] | 49[e] | 6186[c] | 2,065,290 | — |
| 5-y COL | 40–75 | 232[e] | 115[e] | 50[e] | 7392 | 2,398,939 | — |
| 10-y COL with 1-y FIT | 40–75 | 232[e] | 111[e] | 50[e] | 6156[c] | 2,220,918 | — |
| 5-y COL | 40–80 | 232[e] | 115[e] | 50[e] | 7968 | 2,573,170 | — |
| 10-y COL with 1-y FIT | 40–80 | 232[e] | 113[e] | 50[e] | 6950[c] | 2,478,106 | — |
| 3-y COL | 40–75 | 233[e] | 117[e] | 50[e] | 11,091 | 4,755,306 | — |
| 4-Fold CRC risk compared with the general population | | | | | | | — |
| 5-y COL (current surveillance)[b] | 45–75 | 407 | 188 | 86 | 6544 | 124,466 | — |
| 2-y FIT | 45–75 | 347 | 144 | 76 | 2231[c] | –1,533,327[d] | — |
| 2-y FIT | 40–75 | 386 | 150 | 78 | 2413[c] | –1,499,975[d] | — |
| 2-y FIT | 40–80 | 388 | 153 | 80 | 2629[c] | –1,460,334[d] | — |
| 10-y COL | 40–75 | 422[e] | 179 | 83[e] | 4370[c] | –839,755[d] | — |
| 10-y COL | 40–80 | 422[e] | 182[e] | 84[e] | 4932[c] | –687,728[d] | — |
| 1-y FIT | 40–75 | 424[e] | 170 | 84[e] | 3573[c] | –921,593[d] | — |
| 1-y FIT | 40–80 | 425[e] | 172 | 86[e] | 3860[c] | –835,029[d] | — |
| 2× 5-y COL followed by 10-y COL | 40–75 | 430[e] | 184[e] | 85[e] | 5116[c] | –425,250[d] | — |
| 4× 5-y COL followed by 2-y FIT | 40–75 | 438[e] | 175 | 84[e] | 5241[c] | 109,122[d] | — |
| 2× 5-y COL followed by 1-y FIT | 40–75 | 438[e] | 177 | 86[e] | 4874[c] | –25,606[d] | — |
| 2× 3-y COL followed by 1-y FIT | 40–75 | 439[e] | 177 | 86[e] | 5027[c] | 190,042 | — |
| 4× 5-y COL followed by 2-y FIT | 40–80 | 440[e] | 179[e] | 86[e] | 5462[c] | 150,719 | — |
| 2× 5-y COL followed by 1-y FIT | 40–80 | 440[e] | 180[e] | 87[e] | 5164[c] | 60,875[d] | — |
| 4× 5-y COL followed by 10-y COL | 40–75 | 440[e] | 187[e] | 86[e] | 6019[c] | 166,823 | — |
| 2× 3-y COL followed by 1-y FIT | 40–80 | 440[e] | 179[e] | 87[e] | 5316[c] | 275,390 | — |
| 4× 5-y COL followed by 2-y FIT and exit COL | 40–80 | 440[e] | 181[e] | 86[e] | 5900[c] | 264,345 | — |
| 4× 5-y COL followed by 2-y FIT and exit COL | 40–75 | 442[e] | 185[e] | 86[e] | 5924[c] | 244,791 | — |

**Table 2.** Continued

| Test and interval | Start–stop age, *y* | Outcomes per 1000 individuals compared with no surveillance: QALYs gained, n | Prevented, n: CRC cases | Prevented, n: CRC deaths | COLs, n | Costs, € | Optimal strategy[a] |
|---|---|---|---|---|---|---|---|
| 10-y COL with 2-y FIT | 40–75 | 443[e] | 186[e] | 87[e] | 5309[c] | –197,704[d] | — |
| 10-y COL with 2-y FIT | 40–80 | 444[e] | 189[e] | 88[e] | 5976[c] | –2935[d] | Yes |
| 4× 3-y COL followed by 1-y FIT | 40–75 | 444[e] | 181[e] | 86[e] | 6402[c] | 1,084,559 | — |
| 4× 5-y COL followed by 1-y FIT | 40–75 | 445[e] | 184[e] | 86[e] | 5884[c] | 387,107 | — |
| 4× 3-y COL followed by 1-y FIT | 40–80 | 445[e] | 184[e] | 87[e] | 6693[c] | 1,171,020 | — |
| 4× 5-y COL followed by 1-y FIT | 40–80 | 446[e] | 187[e] | 88[e] | 6175[c] | 475,295 | — |
| 4× 5-y COL followed by 1-y FIT and exit COL | 40–80 | 447[e] | 189[e] | 88[e] | 6629[c] | 604,634 | — |
| 4× 5-y COL followed by 1-y FIT and exit COL | 40–75 | 447[e] | 190[e] | 88[e] | 6491[c] | 545,073 | — |
| 5-y COL | 40–75 | 450[e] | 196[e] | 89[e] | 7562 | 821,270 | — |
| 10-y COL with 1-y FIT | 40–75 | 451[e] | 190[e] | 88[e] | 6455[c] | 697,371 | — |
| 5-y COL | 40–80 | 451[e] | 197[e] | 89[e] | 8101 | 984,882 | — |
| 10-y COL with 1-y FIT | 40–80 | 451[e] | 193[e] | 89[e] | 7218 | 939,852 | — |
| 3-y COL | 40–75 | 456[e] | 200[e] | 89[e] | 11,092 | 3,135,126 | — |
| 3-y COL | 40–80 | 457[e] | 203[e] | 90[e] | 12,352 | 3,546,941 | — |

NOTE. Results are presented for the lifetime of a cohort of 1000 individuals starting at age 40 years compared with no surveillance.
See Supplementary Table 8 for an explanation of why strategies do fulfill the criteria regarding CRC cases prevented, but not regarding CRC deaths prevented.
COL, colonoscopy.
[a]The strategy that met all criteria and had the highest gain in QALYs was identified as optimal.
[b]Current surveillance is not a (near-)efficient strategy, but is added to enable comparison.
[c]Strategy with the predicted colonoscopy burden <110% of the predicted colonoscopy burden under current surveillance.
[d]Strategy that is predicted to be not more expensive than current surveillance.
[e]Strategy with noninferior effectiveness compared with current surveillance. Noninferiority effectiveness was defined as preventing at least 95% of the CRC cases and CRC deaths prevented by current surveillance and gaining at least 95% of the QALYs gained by current surveillance.



groups. This is also implied by the high uncertainty surrounding the magnitude of CRC risk in different FH groups in literature.[3–6] However, when more consistent and less uncertain estimates of CRC risk in FH subgroups become available, the potential of personalized surveillance can be re-evaluated.

A key strength of this study is that we have evaluated an extensive range of surveillance strategies, including colonoscopy-based strategies, FIT-based strategies, and strategies in which colonoscopy and FIT are alternated. Furthermore, in order to determine the optimal strategy, we used a multistep decision algorithm that jointly considers multiple outcomes that are relevant to stakeholders in the field. Lastly, a range of sensitivity analyses were conducted to evaluate the impact of major input parameters, such as colonoscopy quality and FIT costs. Results remained robust to changes in most parameters, as in the majority of these analyses, the optimal strategy identified was consistent with the one identified in the main analysis. In the other sensitivity analyses, strategies that were identified as optimal were either strategies in which FIT was combined with colonoscopy or strategies that consisted of FIT only.

However, this study is not without limitations. Firstly, although we adapted the test characteristics of FIT from a threshold of 47 $\mu$g/g to 15 $\mu$g/g using data from a surveillance population, the test characteristics at a threshold of 47 $\mu$g/g have been calibrated against data from a Dutch screening trial. Nevertheless, the results of a meta-analysis did not find a difference in diagnostic performance of FIT in individuals at increased risk of CRC compared with the general population.[30] To explore the influence of FIT sensitivity on the optimal strategy, we performed a sensitivity analysis assuming a 10% lower sensitivity of FIT for AAs. Moreover, we performed a sensitivity analysis assuming a FIT threshold of 10 $\mu$g/g. In both analyses, the optimal strategy was consistent with the one identified in the main analysis. Another important assumption is that we assumed that FIT results were independent of previous FIT results. However, if lesions may be systematically missed by FIT, for example, due to nonbleeding lesions, the effectiveness of strategies including FIT will be overestimated.[31]

Secondly, the ASCCA model, originally developed for individuals at average risk of CRC, was used for all analyses. We adapted this model for individuals with an FH of CRC, and subsequently validated the performance of the ASCCA-FCRC model against the FACTS study. Adaptation was done under 2 scenarios: 1 assuming that the increased CRC risk was due to increased incidence of lesions, and the other assuming that it was due to increased progression of adenomas. The validation

**Table 3.** Optimal Strategy Identified in the Main Analysis and the Sensitivity Analyses

| Variable | Optimal strategy | |
|---|---|---|
| | Test and interval | Start–stop age, *y* |
| 2-Fold CRC risk compared with the general population | | |
| Main analysis | 10-y COL with 2-y FIT | 40–80 |
| Sensitivity analysis | | |
| 30% participation to colonoscopy and 50% to FIT | 1-y FIT | 40–80 |
| 50% participation to colonoscopy and FIT | No optimal strategy identified[a] | — |
| 70% participation to colonoscopy and FIT | 10-y COL with 2-y FIT | 40–80 |
| 70% participation to colonoscopy and 85% to FIT | 10-y COL with 2-y FIT | 40–75 |
| Higher miss rate of colonoscopy for precursor lesions | 10-y COL with 2-y FIT | 40–80 |
| Lower sensitivity of FIT for large adenomas | 10-y COL with 2-y FIT | 40–80 |
| Lower threshold of FIT | 10-y COL with 2-y FIT | 40–80 |
| Lower costs of FIT | 10-y COL with 2-y FIT | 40–80 |
| Increased CRC risk due to increased progression of adenomas | 10-y COL with 2-y FIT | 40–80 |
| 4-Fold CRC risk compared with the general population | | |
| Main analysis | 10-y COL with 2-y FIT | 40–80 |
| Sensitivity analysis | | |
| 30% participation to colonoscopy and 50% to FIT | 1-y FIT | 40–80 |
| 50% participation to colonoscopy and FIT | 1-y FIT | 40–80 |
| 70% participation to colonoscopy and FIT | 2× 5-y COL followed by 1-y FIT | 40–80 |
| 70% participation to colonoscopy and 85% to FIT | 10-y COL with 2-y FIT | 40–80 |
| Higher miss rate of colonoscopy for precursor lesions | 10-y COL with 2-y FIT | 40–80 |
| Lower sensitivity of FIT for large adenomas | 10-y COL with 2-y FIT | 40–80 |
| Lower threshold of FIT | 10-y COL with 2-y FIT | 40–80 |
| Lower costs of FIT | 10-y COL with 2-y FIT | 40–80 |
| Increased CRC risk due to increased progression of adenomas | 2× 3-y COL followed by 1-y FIT | 40–80 |

COL, colonoscopy.
[a]Although no optimal strategy could be identified, yearly FIT from age 40 to 80 years satisfied 3 of the 4 criteria, with an exception for the criterion of CRC cases prevented, as this strategy prevented 93.3% of CRC cases instead of the required 95%.

indicated a superior model fit under the former assumption. Moreover, limited data suggest that CRC risk in this population is increased due to increased lesion incidence.[13] However, it is also plausible that the increased risk may be a consequence of a combination of increased incidence and progression. Under both extreme scenarios that the increased risk is due solely to either assumption, similar strategies were identified as optimal. Hence, if the actual scenario lies between these extremes, we anticipate that the results will remain similar. However, more research into the natural history of CRC in individuals with an FH of CRC is needed.

Finally, in the sensitivity analysis assuming imperfect adherence, the assumption of random participation in testing is likely to overestimate the effectiveness of the strategies with FIT. Under this assumption, most individuals will participate at least once, given the high cumulative number of FITs performed, although in reality, it is likely that a significant proportion of individuals will never participate.[21] Indeed, in the sensitivity analyses with imperfect adherence, strategies with FIT had a more beneficial cost-effectiveness balance than in the analysis with perfect adherence. As a result, the optimal strategy in most analyses with imperfect adherence was a strategy with many FITs performed, consisting of 2 rounds of 5-yearly colonoscopy followed by yearly FIT or 2-yearly FIT.

In conclusion, FIT could play an important role in surveillance by using resources more efficiently without compromising effectiveness compared with colonoscopy surveillance for individuals with an FH of CRC and without a hereditary cancer syndrome, such as polyposis or Lynch syndrome. Ten-yearly colonoscopy with 2-yearly FIT in between colonoscopies from age 40 to 80 years is predicted to be the optimal surveillance strategy. This surveillance strategy is efficient, leads to more QALYs than current 5-yearly colonoscopy surveillance between ages 45 and 75 years, and reduces the colonoscopy burden and costs.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.08.025.

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Gerrit A. Meijer, PhD (Writing – review & editing: Equal; Interpretation of the data: Equal)
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Nicoline Hoogerbrugge, PhD (Conceptualization: Equal; Funding acquisition: Equal; Writing – review & editing: Equal; Interpretation of the data: Equal)
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**Conflicts of interest**
These authors disclose the following: Karen Canfell is co–principal investigator of an investigator-initiated trial of cervical screening, Compass, run by The Australian Centre for the Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity; Compass receives infrastructure support from the Australian government and the ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics. Karen Canfell is also co–principal investigator on a major implementation program, Elimination of Cervical Cancer in the Western Pacific, which has received support from the Minderoo Foundation and equipment donations from Cepheid Inc. Veerle M. H. Coupé and Gerrit A. Meijer have several patents pending and/or issued. Gerrit A. Meijer is co-founder, stockholder, and board member (chief scientific officer) of CRCbioscreen BV, he has a research collaboration with CZ Health Insurances (cash contribution to ZonMW grant), and has research collaborations with Exact Sciences, Sysmex, and Sentinel Ch. SpA Personal Genome Diagnostics (PGDX), DELFi Diagnostics, and Hartwig Medical Foundation; these companies provide materials and equipment for genomic analyses. Evelien Dekker has endoscopic equipment on loan from FujiFilm and has received a research grant from FujiFilm. Evelien Dekker has also received honoraria for consultancy from Olympus, Fujifilm, Ambu, InterVenn, Norgine, and Exact Sciences, and speakers' fees from Olympus, GI Supply, Norgine, IPSEN/Mayoly, and FujiFilm. The remaining authors disclose no conflicts.

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**Data Availability**
Input and detailed output data, as well as codes, can be accessed from the corresponding author upon request with a signed agreement.