# Cost-effectiveness analysis of alternative colorectal cancer screening strategies in high-risk individuals

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## Abstract

**Background and aims:** Current guidelines recommend colonoscopy every 3–5 years for colorectal cancer (CRC) screening of individuals with a familial history of CRC. The objective of this study was to compare the cost effectiveness of screening alternatives in this population.
**Methods:** Eight screening strategies were compared with no screening: *fecal* immunochemical test (FIT), Stool DNA and blood-based screening every 2 years, colonoscopy, computed tomography colonography, colon capsules, and sigmoidoscopy every 5 years, and colonoscopy at 45 years followed, if negative, by FIT every 2 years. Screening test and procedures performance were obtained from the literature. A microsimulation model reproducing the natural history of CRC was used to estimate the cost (€2018) and effectiveness [quality-adjusted life-years (QALYs)] of each strategy. A lifetime horizon was used. Costs and effectiveness were discounted at 3.5% annually.
**Results:** Compared with no screening, colonoscopy and sigmoidoscopy at a 30% uptake were the most effective strategy (46.3 and 43.9 QALY/1000). FIT at a 30 µg/g threshold with 30% uptake was only half as effective (25.7 QALY). Colonoscopy was associated with a cost of €484,000 per 1000 individuals whereas sigmoidoscopy and FIT were associated with much lower costs (€123,610 and €66,860). Incremental cost-effectiveness rate for FIT and sigmoidoscopy were €2600/QALY (*versus* no screening) and €3100/QALY (*versus* FIT), respectively, whereas it was €150,000/QALY for colonoscopy (*versus* sigmoidoscopy). With a lower threshold (10 µg/g) and a higher uptake of 45%, FIT was more effective and less costly than colonoscopy at a 30% uptake and was associated with an incremental cost–effectiveness ratio (ICER) of €4240/QALY *versus* no screening.
**Conclusion:** At 30% uptake, current screening is the most effective screening strategy for high-risk individuals but is associated with a high ICER. Sigmoidoscopy and FIT at lower thresholds (10 µg/g) and a higher uptake should be given consideration as cost-effective alternatives.

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## Plain Language Summary

**Cost-effectiveness analysis of colorectal cancer screening strategies in high-risk individuals**

- Fecal occult blood testing with an immunochemical test (FIT) is generally considered as the most cost-effective alternative in colorectal cancer screening programs for average risk individuals without family history.
- Current screening guidelines for high-risk individuals with familial history recommend colonoscopy every 3–5 years.
- Colonoscopy every 3–5 years for individuals with familial history is the most effective strategy but is associated with a high incremental cost–effectiveness ratio.
- Compared with colonoscopy, if screening based on FIT is associated with a higher participation rate, it can achieve a similar effectiveness at a lower cost.

## Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most deadly in France. The incidence of CRC was 23,216 cases for men and 20,120 cases for women in France for 2018, corresponding to a world-standardized incidence of 34.0/100,000 for men and 23.9/100,000 for women.[1] The mortality for 2015 was 9209 men and 7908 women, or 11.5/100,000 men and 6.9/100,000 women.[1]

Adenocarcinomas account for more than 95% of CRCs. These usually develop from a precancerous lesion: the adenomatous lesion that can form a polyp or plane lesion. The risk of adenoma transforming into cancer depends on its size and histopathological characteristics. The duration of this "adenoma–carcinoma sequence" is on average 10–15 years.[2] The main risk factors for CRC are age greater than 50 years, inflammatory bowel diseases (IBDs), and a personal or family history of adenoma or CRC, genetic predisposition, excessive consumption of red meat or alcoholic beverages, smoking, and obesity.

Given the existence of precancerous lesions, and the better survival of adenocarcinomas diagnosed at an early stage,[3] CRC screening can have associated public health benefits. These benefits were confirmed by a Cochrane meta-analysis in which four randomized clinical trials demonstrated a relative risk reduction in CRC mortality of 16% (95% CI: 10–22%) based on fecal occult blood testing with the Hemoccult II® test.[4]

A population-based nationwide CRC screening program was set up in France from 2009. All individuals aged 50–74 years are initially eligible for the program and are invited by postal mail by the national health insurance to consult their general practitioner to enter the program. However, individuals at high risk (familial history of CRC or IBD) or very high risk [familial polyposis (FAP) or Lynch syndrome] of CRC are currently excluded from the nationwide CRC screening program and are instead subject to tailored opportunistic screening.

Individuals with IBD, FAP, or Lynch syndrome are seen regularly by a gastroenterologist and follow specific guidelines tailored to their chronic condition, making it difficult to include them in a national program. On the other hand, individuals with familial history, defined as at least one first-degree relative with CRC under 50 years, or two or more first-degree relatives with CRC,[5] could be included in the national program if FAP or Lynch families are excluded.

Currently, these individuals are invited despite their familial history as this information is not readily accessible in the national health information system. They are subsequently referred to a gastroenterologist after the identification of familial history, and are monitored by full colonoscopy every 3–5 years depending on the results of the first colonoscopy and the familial history.[6] During this two-step process, individuals are at risk of being lost to follow-up, and thus not benefiting from any screening despite their higher risk of CRC. Furthermore, as these individuals are excluded from the national program, no estimate of their screening coverage is currently available even though this population represents 10–15% of the population initially eligible for the national CRC screening program.[7]

Previous studies in the French[8–10] and international contexts[11–13] suggested that annual or biannual fecal occult blood testing with an fecal immunochemical test (FIT) has been shown to be cost saving or has been associated with an incremental cost–effectiveness ratio (ICER) below €30,000/QALY compared with colonoscopy every 10 years, with higher participation rates (42% *versus* 22% for colonoscopy). Therefore, the current national screening program is based on FIT. However, FIT could also be considered a cost-effective alternative to full colonoscopy for individuals with common familial history (FH), enabling the national program to be extended to these individuals. The objective of this work is to compare the cost effectiveness of screening alternatives with colonoscopy currently available in the French context for individuals with FH.

**Table 1.** Screening strategies included in the base case analysis.

| Strategy | Screening test | Frequency | Participation (%) | Age interval |
|---|---|---|---|---|
| Colonoscopy | Colonoscopy | 5 years | 30 | 45–74 |
| FIT (30 μg/g) | FIT (OC-Censor® with 30 μg/g threshold) + colonoscopy if positive | 2 years | 30 | 45–74 |
| Blood-based | Blood-based screening (mSEPT9) + colonoscopy if positive | 2 years | 65 | 45–74 |
| Fecal DNA | Multitarget stool DNA + colonoscopy if positive | 2 years | 30 | 45–74 |
| CTC | CTC + colonoscopy if positive | 5 years | 30 | 45–74 |
| Colon capsules | Second-generation colon capsules + colonoscopy if positive | 5 years | 30 | 45–74 |
| Sigmoidoscopy | Sigmoidoscopy + colonoscopy if positive | 5 years | 30 | 45–74 |
| FIT (30 μg/g) after negative colonoscopy | Colonoscopy | Once | 30 | 45 |
| | If negative, FIT (OC-Censor® with 30 μg/g threshold) | 2 years | 30 | 47–74 |

CTC, computed tomography colonography; FIT, fecal immunochemical test.

## Methods

### Population, setting and perspective

The results were obtained for a cohort of individuals aged 45 years with FH of CRC representative of the French population (50% male). These individuals excluded FAP or Lynch syndrome. Cost and effectiveness results were obtained for the French context. Cost included only direct medical cost valued from the societal perspective (i.e. national health insurance, government funding and out-of-pocket costs). Effectiveness was based on quality-adjusted life-years (QALYs) with utilities valued from the societal perspective.

### CRC screening strategies

Eight screening strategies, including the current guidelines for individuals with FH of CRC that includes full colonoscopy every 5 years, were compared with no screening (Table 1). Screening started from age 45 years to 74 years as is recommended for individuals with FH.[14] This age is in line with current practice in France.

All strategies included a screening test followed by a full colonoscopy when the test was positive. Screening tests included fecal occult blood testing based on either OC-Censor®, blood-based screening based on the mSEPT9 marker,[15] or multitarget stool DNA testing[16] every 2 years. They also included colonoscopy, computed tomography colonography (CTC), second-generation colon capsules, or sigmoidoscopy every 5 years. The final strategy was based on a colonoscopy at 45 years followed by OC-Censor® every 2 years if negative.

Screening strategies were compared for a participation rate of 30% based on the observed compliance with screening guidelines in France in the high-risk population.[17] We did not assume any differences in participation between strategies to facilitate result interpretation, except for blood-based strategies with an assumed 65% participation rate. Assumptions regarding a higher participation for FIT strategies were tested in sensitivity analysis. The probability of participation at each screening cycle was varied stochastically between individuals based on previous participation, age, and sex[18–20] in order to better capture real-world participation structure. Individuals with a positive screening test were referred for follow-up colonoscopy. It was assumed, based on data from the French screening program, that 11.1% were lost to follow-up and did not undergo colonoscopy.[20] If negative, individuals did not undergo screening for the next 5 years. Individuals

with adenomas that were detected and removed were assumed to undergo colonoscopy monitoring as per French guidelines (i.e. every 3–5 years depending on the number of adenomas, sizes, and grade). Assumptions were made for the grade distribution for adenomas <10 mm.[21] It was assumed that monitoring continued until the diagnosis of colorectal cancer or 80 years. Compliance with the recommended follow-up and monitoring was set to 31% based on data for high-risk patients in France.

### Time horizon and discount rate

A lifetime time horizon was used as screening reduces the incidence of cancers or cancer-related complications that can appear years after screening. A 3.5% discount rate was used for both cost and effectiveness as per French guidelines at the time of the study.[22]

### CRC screening strategies' effectiveness

The effectiveness of screening strategies directly depended on screening test performances. These were based on a systematic literature review and are detailed in Table 2. For stool-based tests, we assumed that adenomas smaller than 10 mm was not detectable as true positives given that sensitivity and specificity are reported for advanced adenomas and CRC only.[16,23] A threshold of 30 μgHb/g was used for the OC-Sensor® test, as this is the threshold currently used in the French context. However, the study by Hol *et al.* (2009), comparing the performance of different thresholds for OC-Sensor® was used to extrapolate the specificity and sensitivity of OC-Sensor® for different thresholds tested in sensitivity analysis.[24] These thresholds included 20, 15 and 10 μgHb/g of feces. Lower thresholds were associated with higher sensitivity at the expense of lower specificity. Higher sensitivity was thought to be desirable for individuals with FH. For blood-based tests, we assumed that only CRC was detectable.[15] For colon capsule, CTC, colonoscopy, and sigmoidoscopy, sensitivity depended on the size of the adenomas,[25–28] with only colonoscopy and sigmoidoscopy capable of detecting adenomas smaller than 5 mm. It was assumed that sigmoidoscopy would have the same performance as colonoscopy but could only detect distal lesions. Patients undergoing colon capsule, CTC, and colonoscopy were assumed to be at risk of serious complications[29–32] (Table 2).

### Utilities and cost

Baseline utilities were adjusted for age.[33] CRC-related health status was associated with poorer utilities based on the literature.[34] Serious complications were associated with disutility.[35] Both were based on non-French populations as no data for the French context was identified in the literature.

Table 3 details the cost and utilities used in this study. Screening tests were based on current costs of the national screening program, prices published by national health insurance, or assumptions for tests not currently marketed in France. The costs of complications were based on the relevant diagnosis-related group codes. CRC-related costs were based on French cost of illness study[36] that estimated the overall cost of CRC-related care (both inpatient, including chemotherapy sessions, and outpatient care) by cancer stage, differentiating the first and subsequent years of care. Fixed costs related to the screening program were not included as they were assumed to be similar across all screening strategies.

All costs are reported in 2018 euros. When necessary, costs were updated for the year 2018 using the price index for healthcare goods published by the National Institute of Statistics and Economic Studies.

### Model structure and assumptions

The model simulates the natural history of CRC in a cohort of 5,000,000 individuals from birth to death as described previously.[41] Detailed assumptions and model structure are available in the Supplemental Material online. In summary, it is based on the adenoma-carcinoma sequence, with the incidence of adenomas and the risk of CRC progression calibrated on adenoma prevalence data in the autopsy series[42,43] and on CRC incidence in France.[44]

Familial history, excluding FAP or Lynch syndromes, is recognized as a risk factor for CRC. However, where CRC natural history is generally understood and well described in FAP or Lynch syndromes, there is only a general understanding of CRC natural history in individuals with FH. CRC in individuals with FH are probably related to both genetic and shared environmental risks, with no evidence for differential adenoma location or adenoma progression by family history.[45]

**Table 2.** Test performance and associated complication rate.

| Test | | |
|---|---|---|
| FIT (30 µg/g) | Se: CRC 75.0% AA: 30.0% | Robertson *et al.*[23] adjusted with Hol[24] |
| | Sp: 96.6% | |
| FIT (20 µg/g) | Se: CRC 80.6% AA: 31.5% | Robertson *et al.*[23] adjusted with Hol[24] |
| | Sp: 95.8% | |
| FIT (15 µg/g) | Se: CRC 80.6% AA: 34.9% | Robertson *et al.*[23] adjusted with Hol[24] |
| | Sp: 95.0% | |
| FIT (10 µg/g) | Se: CRC 92.3% AA: 41.6% | Robertson *et al.*[23] adjusted with Hol[24] |
| | Sp: 92.9% | |
| Stool DNA | Se: CRC 92.3% AA: 42.4% | Imperiale *et al.*[16] |
| | Sp: 86.6% | |
| Blood-based | Se: CRC 66.0% | Yan *et al.*[15] |
| | Sp: 91.0% | |
| Colonoscopy | Se: CRC: 95% >6 mm: 90% ≤6 mm: 45% | HAS[25] |
| | Sp: 95% | |
| CTC | Se: CRC: 84% >10 mm: 76% ≤6 mm: 44% | HAS[26] and Weinberg *et al.*[27] |
| | Sp: 89% | |
| Colon capsule | Se: CRC: 87% >10 mm: 86% ≤6 mm: 87% | HAS[26] and Spada *et al.*[28] |
| | Sp: 92% | |
| Sigmoidoscopy | Equal to colonoscopy for distal lesions only | Assumptions |
| **Severe complications** | | |
| Colonoscopy | No resection | Denis *et al.*[30], Reumkens *et al.*[29] |
| | Bleeding: 0.06% | |
| | Perforation: 0.04% | |
| | Others: 0.04% | |
| | Resection | |
| | Bleeding: 0.98% | |
| | Perforation: 0.08% | |
| | Others: 0.10% | |
| Colon capsule | Retention: 0.03% | ESGE[31] |
| CTC | Perforation: 0.04% | Bellini *et al.*[32] |

AA, advanced adenoma; CRC, colorectal cancer; CTC, computed tomography colonography; ESGE, European Society of Gastrointestinal Endoscopy; FIT, fecal immunochemical test; HAS, Haute Autorité de Santé; Se, sensitivity; Sp, specificity.

**Table 3.** Model parameters.

| Parameter | Value | Source |
|---|---|---|
| **Population** | | |
| Individuals with familial history (% of the total eligible population) | At least one first degree relative with CRC under 60: 1.1%<br>At least one first degree relative with CRC over 60: 10.3%<br>At least two first degree relatives: 0.6% | Castiglione et al.[7] |
| **Natural history** | | |
| Relative risk of CRC in individuals with familial history | At least one first degree relative with CRC under 60: 1.85<br>At least one first degree relative with CRC over 60: 1.47<br>At least two first degree relatives: 2.60 | Lowery et al.[37] |
| **Screening** | | |
| OR of participating | Female: 0.9<br>Age<br>55–59   1.32<br>60–64   1.58<br>65–69   1.75<br>70–74   1.95 | Pornet et al.[18] |
| Probability of participating | 30% | Ait Ouakrim et al.[17] |
| OR of reparticipating | Female: 1.43<br>Age<br>55–59   1.59<br>60–64   1.95<br>65–69   2.17<br>70–74   1.89 | Pornet et al.[19] |
| **Utilities** | | |
| CRC | I: 0.74<br>II: 0.74<br>III: 0.67<br>IV: 0.25 | Ness et al.[34] |
| Severe complications | 0.128 | Andersson et al.[35] |
| **Costs (2018 euros)** | | |
| Invitation to the program per individual | 1.00 | Based on national screening program data |
| FIT* | 14.34 | National health insurance |
| Stool DNA test* | 236.88 | Based on Ladabaum[38] |
| Blood-based test | 125.13 | Based on Ladabaum[39] and national health insurance |
| Colonoscopy | Without adenoma removal 806.44<br>With adenoma removal 1191.60 | National health insurance |
| Sigmoidoscopy | 96.34 | National health insurance |
| CTC | 95.41 | National health insurance |
| Colon capsule | 510.24 | National health insurance |
| Bleeding | 1241.09 | DRG cost |
| Perforation | 2810.20 | DRG cost |
| Retention | 1241.09 | DRG cost |
| Other sever complications | 6621.47 | DRG cost |

*(Continued)*

**Table 3.** (Continued)

| Parameter | Value | Source |
|---|---|---|
| CRC related-cost | Year 1, by stage<br>I 13,062.00<br>II 16,815.88<br>III 23,609.35<br>IV 28,173.74<br>Subsequent years<br>I 0.00<br>II 578.76<br>III 812.57<br>IV 969.67 | IRDES[36], national disease cost study[40] |
| Age-related baseline utilities | 40–49   1<br>50–59   0.95<br>60–69   0.94<br>70–79   0.9<br>80+    0.88 | Perneger *et al.*[33] |

*Including distribution cost.
CRC, colorectal cancer; DRG, diagnosis-related group; CTC, computed tomography colonography; DRG, ; FIT, fecal immunochemical test; OR, odds ratio.

Thus, it was assumed that the elevated CRC incidence was entirely due to elevated adenoma incidence. Based on these assumptions, the higher incidence of CRC in individuals with FH[37] was obtained by calibrating the incidence rate of adenomas to reproduce observed CRC incidence rates in individuals with FH.

*Analytical methods*
Strategies were sorted by increasing effectiveness (QALY) with incremental cost–effectiveness ratios (ICERs) calculated for all non-dominated or non-extended dominated strategies. Scenario analysis was performed with alternative participation and positivity threshold for FIT (Table 4). ICERs were reestimated for all included strategies with the modified FIT strategy. Deterministic and probabilistic sensitivity analyses were performed. Details for parameter uncertainty are provided in the Supplemental Material. Strategies were considered cost-effective if their ICER fell under the willingness to pay (WTP) threshold. A WTP threshold of €40,000/QALY was used.

The model was programmed in C++ as a library for Microsoft Excel. The model was run until all simulated individuals were deceased.

## Results
Figure 1 shows the results for the comparison of screening strategies for individuals with FH.

The current screening strategy based on full colonoscopy every 5 years was associated with 741.4 per 100,000 cumulative CRC incidence over high-risk patients' lifetime and 348.1 per 100,000 CRC related deaths for 120,800 colonoscopies performed per 100,000 individuals (Supplemental Table 2). It was the most effective for an added 219.8 undiscounted or 46.3 discounted QALY compared with no screening per 1000 individuals. Comparatively, the FIT-based strategy was associated with only 123.7 undiscounted or 25.7 discounted QALY, less than half as effective after discounting, and 190.5 undiscounted or 39.8 discounted QALY when performed after a negative colonoscopy. Sigmoidoscopy was associated with 208.4 undiscounted or 43.9 discounted QALY, making it the second most effective strategy. In terms of costs, colonoscopy was the second most costly strategy with an increase in total cost of €618.14 undiscounted or €484.00 discounted per individual compared to no screening, after blood-based testing (€1,126.09 undiscounted and €667.03 discounted compared to no screening). Comparatively, sigmoidoscopy was associated with a decrease of only €13.5 in undiscounted costs or an increase of €123.61 in discounted and FIT with increase of €3.01 in undiscounted and €66.86 in discounted costs.

FIT and sigmoidoscopy were associated with an ICER of €2,600/QALY and €3,100/QALY compared with no screening and FIT respectively, whereas the strategy based on colonoscopy was

**Table 4.** Scenario analysis.

| Strategy (*versus* no screening) | Disc. QALY (per 1000 individuals) | Disc. costs (€) | ICER* (€/QALY) |
|---|---|---|---|
| FIT (10 µg/g) – 30% participation | 36.5 | 104.68 | Weakly dominated |
| FIT (15 µg/g) – 30% participation | 33.8 | 85.95 | 2,543 |
| FIT (20 µg/g) – 30% participation | 25.9 | 73.59 | Weakly dominated |
| FIT (30 µg/g) – 30% participation | 25.7 | 66.86 | 2,602 |
| FIT (10 µg/g) – 45% participation | 58.4 | 150.75 | 4,240 |
| FIT (15 µg/g) – 45% participation | 48.9 | 122.76 | 2,510 |
| FIT (20 µg/g) – 45% participation | 42.3 | 104.27 | 2,465 |
| FIT (30 µg/g) – 45% participation | 44.9 | 93.51 | 2,083 |
| FIT (10 µg/g) after negative colonoscopy – 30% participation | 43.2 | 448.71 | Dominated |
| FIT (15 µg/g) after negative colonoscopy – 30% participation | 42.2 | 435.06 | Dominated |
| FIT (20 µg/g) after negative colonoscopy – 30% participation | 41.3 | 430.40 | Dominated |
| FIT (30 µg/g) after negative colonoscopy – 30% participation | 39.8 | 424.92 | Dominated |
| FIT (10 µg/g) after negative colonoscopy – 45% participation | 61.1 | 573.49 | 151,000 |
| FIT (15 µg/g) after negative colonoscopy – 45% participation | 57.8 | 552.10 | Dominated |
| FIT (20 µg/g) after negative colonoscopy – 45% participation | 57.7 | 544.48 | Dominated |
| FIT (30 µg/g) after negative colonoscopy – 45% participation | 53.8 | 534.06 | Dominated |

*ICERs were estimated by replacing the correspond strategy (either FIT or FIT after negative colonoscopy) in the base case analysis, and estimating the efficiency frontier by comparing all strategies with each other and excluding dominated and extended dominated strategies.
Disc., discounted; FIT, fecal immunochemical test; ICER, incremental cost–effectiveness ratio; QALY, quality-adjusted life-year.

associated with an ICER of €150,000/QALY compared with sigmoidoscopy. All other strategies were dominated.

Table 4 shows the results of the alternative scenarios compared.

Using a lower threshold improved the effectiveness of the FIT strategy. At 10µg/g, the FIT strategy was associated with a 74.7 undiscounted or 10.8 discounted QALY increase per 1000 individuals compared with 30µg/g, increasing the effectiveness of this strategy to 198.1 undiscounted or 36.5 discounted QALY compared with no screening. FIT at 10µg/g after a negative colonoscopy was associated with 225.2 undiscounted or 43.2 discounted QALY compared with no screening, almost as effective as sigmoidoscopy but less than colonoscopy when considering discounted QALY but for a total cost of €524.1 undiscounted or €448.71 discounted compared with no screening, similar to

colonoscopy. Regardless of the threshold, at similar participation rates, all these alternative strategies did not change the efficiency frontier.

The assumption that stool-based strategies were associated with a higher participation than colonoscopy (45% *versus* 30%) produces very different results (Table 4). FIT at 30µg/g with 45% participation has a similar effectiveness to colonoscopy at 30% participation. It was also associated with a much lower cost. FIT at 10µg/g is more effective and less costly, dominating colonoscopy. In this analysis, it is associated with an ICER of €4,240/QALY compared with no screening. Similarly, FIT after negative colonoscopy at 45% participation is more effective than colonoscopy only at 30% participation regardless of the threshold, with an incremental effectiveness compared with no screening of 61.1 discounted QALY per 1000 individuals that is about 50% more effective than colonoscopy. It is, however,
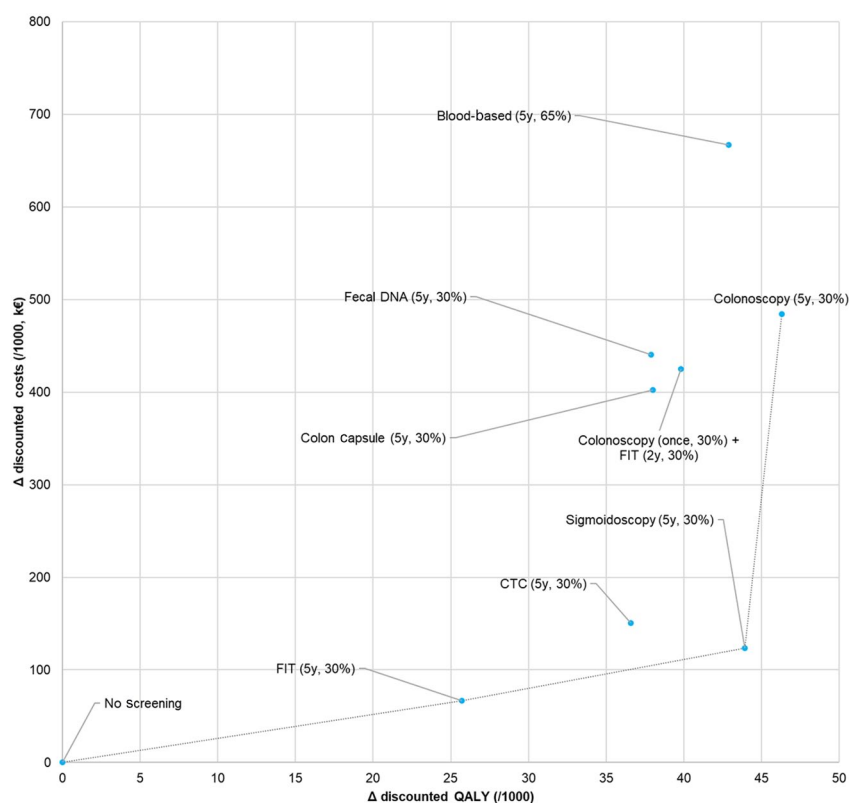
**Figure 1.** Cost-effectiveness plane for alternative screening strategies for high-risk individuals.
*A*y, *XX*% = every *A* years with *XX*% average uptake.
CTC, computed tomography colonography; FIT, fecal immunochemical test; QALY, quality-adjusted life-year.

associated with an ICER of €151,000/QALY compared with FIT alone.

## Discussion

In the French context, for individuals at a high risk of CRC due to FH (excluding FAP and Lynch syndromes), and given a 30% participation rate, the current screening strategy based on full colonoscopy from 45 years is the most effective strategy for QALY. At similar participation rates, FIT, regardless of the positivity threshold, has a lower efficacy than colonoscopy. Only the strategy based on sigmoidoscopy every 5 years is approximately as effective as colonoscopy. In terms of costs, the strategy based on colonoscopy is many times costlier than FIT or sigmoidoscopy, resulting in an ICER of over €150,000/QALY *versus* sigmoidoscopy.

Few cost-effectiveness studies have specifically looked at individuals with common FH. Most studies focus on average-risk individuals,

excluding high-risk individuals, and have found annual or biennial FIT to be cost-saving or very cost-effective compared with colonoscopy every 10 years.[11–13] We found that in individuals with common FH, FIT every 2 years is also associated with a lower ICER than colonoscopy every 5 years but with a clinically significant difference in QALY that is not observed in average-risk studies. Similar results were reported for Australia, with FIT every 2 years being half as effective as colonoscopy every 5 years.[46] Indeed, studies looking at high-risk individuals do not even include FIT[47,48]

In the French context, moving to a less effective, albeit more efficient, strategy is seldom considered, which would leave colonoscopy as the main strategy for individuals with FH at a 30% participation rate. The key factor is thus whether a FIT-based strategy can achieve a higher uptake than colonoscopy. Indeed, results for the French national program show that, for average-risk individuals, participation with FIT is about 34%, higher than the 30% screening rates for

individuals with FH.[20] Studies looking at factors predicting participation in France showed that FH should be associated with a higher willingness to participate.[49,50] It can thus be hypothesized that the low participation in high-risk patients is partly related to a low acceptability of undergoing colonoscopy given its associated high burden (preparation, anesthesia, day hospitalization for individuals still in the workforce). Hence, a FIT-based strategy might be associated with higher participation, in which case, the results suggest that FIT with a lower positivity threshold might outperform colonoscopy in terms of both effectiveness and cost. If the assumption of high participation were to be verified, it would enable the national screening program to be extended to high-risk individuals. At the very least, the results suggest that FIT is an effective strategy for high-risk subjects and should be offered to those failing to comply with colonoscopy.

Assumptions were required to model individuals with common FH. Because CRC natural history in this group is not well described, we relied on a model of CRC natural history for average-risk individuals and on the assumption that elevated CRC incidence was entirely due to elevated adenoma incidence with no difference in adenoma progression by family history. This assumption was supported by observational data,[45] as well as the opinion of the scientific board. This assumption was also based on individuals with first-degree relatives with colonic adenomas showing a similar increase in CRC incidence.[51–54] This suggests that, for these individuals, increased CRC incidence is probably linked to an increased adenoma risk. Conversely, many guidelines for CRC screening include first-degree relatives with adenomas as a risk factor.[14,55]

Because the model relies on the average-risk population model it also suffers the same limitations. In particular, the model does not include serrated adenomas in the natural history of the disease, due to the lack of data on natural history, epidemiology and test performance for these lesions. Serrated adenomas could represent 15–20% of CRC.[56] The weight of serrated adenomas in interval cancers[56–59] and their more difficult detection with colonoscopy[60,61] suggest that their inclusion in the model would decrease the effectiveness of the colonoscopy-based strategy. Similarly, several studies suggest that FIT would have reduced performance for these lesions[62,63]

and results from Greuter *et al.*[64] showed up to a 12% reduction in FIT-based screening effectiveness on CRC incidence when including the serrated pathway. However, the effect of including serrated adenomas on the relative performance of the included strategies is difficult to assess.

There is also uncertainty around the performance of the different tests, although the sensitivity analyses carried out previously showed low sensitivity of the results to these parameters.

The lack of specific data for individuals with FH in France, as these individuals are excluded from the national program, did not allow us to directly validate the results against observed French data. However, the average-risk model was validated for the average-risk population[41] (Supplemental material), and as the CRC incidence in the model reproduced the higher CRC incidence seen in individuals with FH,[37] we considered the model validated for this population.

Finally, we did not include indirect costs in the analysis. Current French guidelines on cost-effectiveness analysis do not recommend including indirect costs because of the large uncertainties associated with the estimation and valuation of indirect costs, with no methodologies considered a gold standard.[22] As a consequence it is likely that the ICERs are overestimated. CRC is likely to have a significant impact on loss of productivity related to surgical treatments, chemotherapies, and as a result of early mortality. As screening effectiveness is based on reducing CRC incidence, more effective strategies such as colonoscopy would lead to a significant reduction in indirect costs.

In conclusion, these results show that at a participation rate of 30%, 5-year colonoscopy and sigmoidoscopy are the most effective screening strategy in individuals with common FH of CRC. If higher participation rates can be achieved with FIT, then FIT at a threshold of 10 µg/g of feces could achieve a similar effectiveness than colonoscopy and sigmoidoscopy and should be considered a cost-effective alternative based in individuals with FH. In the French context, having a single strategy for average-risk individuals and individuals with FH could be an effective way to include individuals with FH in the national screening program, reduce complexity, and possibly improve participation rates in high-risk individuals.

## Ethics statement
This article does not contain any studies involving human participants performed by any of the authors, therefore no ethics approval was not sought.

## Informed consent
This article does not contain any studies involving human participants performed by any of the authors, therefore no informed consent was needed.

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## Supplemental material
Supplemental material for this article is available online.

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