Therapeutic Advances in Gastroenterology   *Original Article*

Cost-effectiveness analysis of alternative colon cancer screening strategies in the context of the French national screening program

Stéphanie Barré, Henri Leleu (iD)**, R. Benamouzig, Jean-Christophe Saurin, Alexandre Vimont, Sabrine Taleb and Frédéric De Bels**

Abstract

Background: A nationwide colorectal cancer (CRC) screening program was set up in France from 2009 for average-risk, asymptomatic people aged 50–74 years based on an immunochemical fecal occult blood test [faecal immunochemical test (FIT)] every 2 years, followed by colonoscopy if positive. The European standard recommends a participation rate of 45% for the program to be cost-effective, yet the latest published rate in France was 34%. The objective of this study was to compare the cost effectiveness of screening alternatives taking real-world participation rates into account.

Methods: Eight screening strategies were compared, based either on a screening test (Guaiac or FIT testing, blood-based, stool DNA, computed tomography colonography, colon capsules, and sigmoidoscopy) followed by full colonoscopy if positive or direct colonoscopy. A microsimulation model was used to estimate the cost effectiveness associated with each strategy.

Results: Compared with no screening, FIT was associated with a 14.0 quality-adjusted life year (QALY) increase of €50,520 per 1000 individuals, giving an incremental cost-effectiveness ratio (ICER) of €3600/QALY. Only stool DNA and blood-based testing were associated with a QALY increase compared with FIT, with stool DNA weakly dominated by blood-based testing, and the latter associated with an ICER of €154,600/QALY compared with FIT. All other strategies were dominated by FIT.

Conclusion: FIT every 2 years appears to be the most cost-effective CRC screening strategy when taking into account a real-world participation rate of 34%.

Keywords: colorectal cancer, cost-effectiveness, screening, FIT

Correspondence to:
Henri Leleu
Public Health Expertise,
157 Rue du Faubourg
Saint-Antoine, Paris,
75011, France
**Henri.leleu@ph-
expertise.com**

**Stéphanie Barré
Sabrine Taleb
Frédéric De Bels**
Institut National du
Cancer, Boulogne, France

R. Benamouzig
Department of
Gastroenterology, Hôpital
Avicenne (AP-HP),
Bobigny, France

Jean-Christophe Saurin
Department of Endoscopy
and Gastroenterology,
Pavillon L, Edouard Herriot
Hospital (Hospices Civils
de Lyon), Lyon, France

Alexandre Vimont
Public health expertise,
Paris, France

Key summary
- FIT is generally considered as the most cost-effective alternative in colon cancer screening programs in international studies.
- Current French colon cancer screening programs for average risk individuals is based on FIT, but with a participation rate of only 34% below the 45% recommended threshold, cost effectiveness is unknown.
- FIT, at a 34% participation rates, is also the most cost-effective alternative in the French context.
- FIT appears to be cost-effective regardless of participation rates.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most deadly in France. The projected incidence of CRC was 23,535 cases for men and 19,533 cases for women in France for 2015.[1] The projected mortality for 2015 was 9337 men and 8496 women.[1]

Adenocarcinoma accounts for more than 95% of CRCs.[2] These usually develop from an 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.[3] The main risk factors for CRC are age greater than 50 years, inflammatory bowel diseases (IBD), 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,[4] CRC screening can have associated public health benefits. These benefits were confirmed by a Cochrane meta-analysis in which four randomised clinical trials demonstrated a relative risk reduction in CRC mortality of 16% [95% confidence interval (CI): 10–22%] based on faecal occult blood testing with the Hemoccult II® test (gFOBT).[5]

A nationwide CRC screening program was set up in France from 2009. The current CRC screening program is for average risk, asymptomatic people aged 50–74 years. Average risk is defined in the program as any individual aged 50–74 years with no personal or familial history of CRC. Familial history was defined as at least one first-degree relative with CRC under 65 years, or two or more first-degree relatives with CRC. The program was initially based on gFOBT. This test was replaced in 2015 by the OC-Sensor® immunoassay. This fecal immunochemical test (FIT) is more sensitive, more reliable and easier to use than gFOBT. Eligible individual aged 50–74 received a mail invitation every 2 years from the national health insurance to perform CRC screening. Individuals must visit their general practitioner (GP), who will screen the individuals from exclusion criteria (in particular personal or familial history of CRC, bowel inflammatory diseases), provide a FIT kit and give an explanation on how to use the test.

The kit includes a prestamped letter for the individuals to send back the FIT test after use. Individuals with a positive occult blood test are referred for a full colonoscopy to screen for cancer or adenomas.[6]

Individuals at high risk (familial history of CRC or IBD) or very high risk [familial polyposis (FAP) or Lynch syndrome] are subject to specific opportunistic individual screening recommendations, and are therefore not included in the current nationwide screening program.

The European standard recommends a participation rate of 45% for the program to be cost-effective.[7] This rate is based on the lower bound of the participation rates in the FOBT clinical trial and is thus considered the minimum acceptable uptake for which there is evidence that screening is effective. The participation published for the latest screening period (2016–2017) showed a rate of 34%, lower than the current 45% objectives.[8] Given the modest sensitivity of a single FIT, this has raised some concern that, at the current participation rate, a strategy based on FIT might not be the most cost-effective alternative.

Previous studies in the French and international contexts have suggested that FIT is a more cost-effective alternative in screening programs.[9–14] Annual or biannual FIT has been shown to cost-saving or very cost-effective compared with colonoscopy every 10 years, with higher participation rates (42% *versus* 22% for colonoscopy). However, these studies were not based on the real-world screening uptake from a national screening program, and usually did not include all current screening alternatives in particular newer tests including blood-based screening (mSEPT9), or multitarget stool DNA testing, computed tomography colonography (CTC) and second-generation colon capsules.[15]

The objective of this work is to compare the cost effectiveness of screening alternatives currently available for average-risk individuals.

Methods

Eight screening strategies were compared with no screening. Seven strategies included a screening test followed by a full colonoscopy when the test was positive – the final strategy being based on full colonoscopy only. Screening tests included
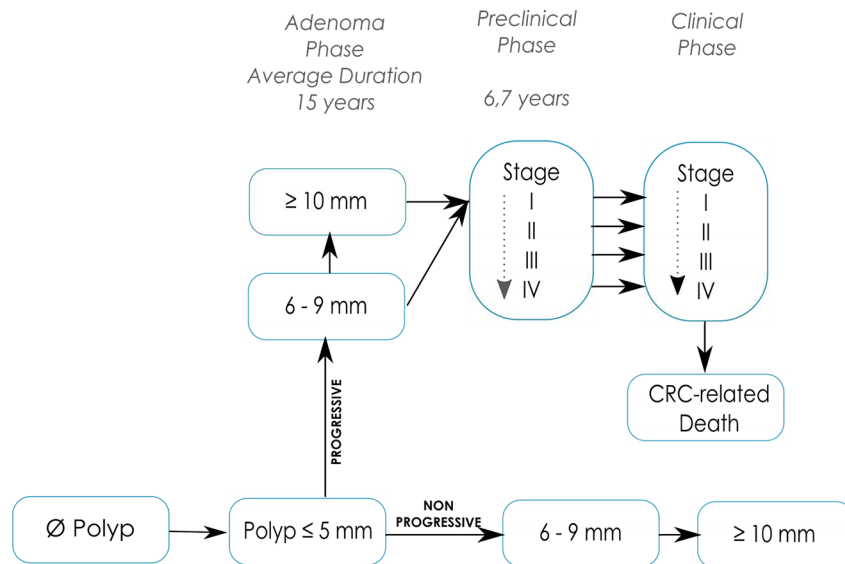
Figure 1. Natural history of development of adenomas in the colon and the adenoma-carcinoma sequence. CRC, colorectal cancer.

faecal occult blood testing based either on the Hemocult® II or OC-Sensor®, blood-based screening based on the mSEPT9 marker,[16] or Multitarget Stool DNA Testing every 2 years.[15] They also included CTC, second-generation colon capsules or sigmoidoscopy every 10 years.

Results were obtained for a population based on the French population entering the CRC screening program that included individuals aged 50 years (50% men) with no prior history of screening, and no familial history of CRC, IBD, FAP or Lynch syndrome.

Cost and effectiveness of the screening strategies were obtained using a microsimulation model constructed and validated to the French context.

Model structure
The model simulates the natural history of CRC in a cohort of 5,000,000 individuals from birth to death.

The natural history is based on the development of adenomas in the colon and the adenoma-carcinoma sequence (Figure 1). Simulated individuals may have no, one or more adenomas during their lifetime. The number of adenomas depended on the individual's baseline risk and the incidence of adenomas by age and sex. Each adenoma is associated with a localisation in the colon based on French CRC incidence data.[17] All adenomas initially appear ≤5 mm and are associated with a probability of developing into CRC. The probability varied stochastically between individuals. It depended on the age at adenoma onset and the sex of the individual. The incidence of adenomas by age and sex, and the mean probability of progression were estimated by calibrating the model. Model calibration was based on adenoma prevalence data in the autopsy series and on CRC incidence in France.[18–20] Adenomas that will develop into CRC progress from adenocarcinoma *in situ* to the metastatic stage if not diagnosed clinically at an earlier stage. The probability of being diagnosed clinically for each stage has been calibrated on the distribution of clinical stages in the French incident population.[20] Finally, CRC is associated with a cancer-specific mortality that depends on the clinical stage at diagnosis and is based on the observed survival data in France.[21,22] The adenoma dwell time and the preclinical sojourn time varied stochastically by individuals and was based on the parameters and assumptions used in the MISCAN model.[18,23] The model also takes into account mortality from causes other than CRC, based on French mortality rates and causes of death. Table 1 shows all the parameters used in the simulation.

Table 1. Parameters.

Parameter	Value	Source
Natural History		
Incidence of adenomas	Based on age and sex	Calibrated
Location of adenomas in the colon	Proximal: 19.4% Distal: 80.6%	National Data on CRC Epidemiology[17]
Likelihood of an adenoma progressing to CRC	Based on age at onset and sex	Calibrated
Time of progression of adenoma to preclinical CRC	Average of 15 years (exponential distribution)	Based on MISCAN publication[18]
Time of progression from preclinical to clinical CRC	Average of 6.7 years (exponential distribution)	Based on MISCAN publication[23]
Distribution of stages at diagnosis	I: 17% II: 31% III: 22% IV: 30%	National Epidemiological Study[17]
Stage I net survival at age <75 years and excluding right colon	Year 1: 98% Year 5: 96% Year 10: 95%	Estimated from a National Epidemiological Study on Cancer Survival[17]
Relative risk of death at 5 years by stage, age at diagnosis and location	Stage I: Ref, II: 2.8, III: 8.4, IV: 30.3 Age >75 years: 1.3 Right Colon: 1.2	Faivre-Finn *et al.*, 2002[21]
Screening		
OR of participating	Female: 0.9 Age 55 59 1.32 60 64 1.58 65 69 1.75 70 74 1.95	Pornet *et al.*, 2010[31]
Probability of participating	45%	Calibrated on participation rank observed in the 2012–2013 national screening campaign
OR of reparticipating	Female: 1.43 Age 55 59 1.59 60 64 1.95 65 69 2.17 70 74 1.89	Pornet *et al.*, 2014[32]
Utilities		
CRC	I: 0.74 II: 0.74 III: 0.67 IV: 0.25	Ness *et al.*, 1999[26]
Severe complications	0.128	Andersson *et al.*, 2013[27]

(Continued)

Table 1. (Continued)

Parameter	Value	Source
Costs (€)		
Invitation to the program per individual	1	Based on national screening program data
gFOBT*	12.14	National Health Insurance
FIT*	14.34	National Health Insurance
Stool DNA test*	236.88	Based on Ladabaum and Mannalithara, 2016[33]
Blood-based test	125.13	Based on Ladabaum and Mannalithara, 2016[33] and National Health Insurance
Colonoscopy	Without adenoma removal 806.44 With adenoma removal 1191.6	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 severe complications	6621.47	DRG Cost
CRC related-cost	Year 1, by stage I 13,062.00 II 16,815.88 III 23,609.35 IV 28,173.74 Subsequent years I 0.00 II 578.76 III 812.57 IV 969.67	IRDES, 2006[45] National disease cost study

*Including distribution cost.
AA, advanced adenoma; CRC, colon cancer; CTC, computed tomography colonography; FIT, faecal occult blood testing with immunoassay; gFOBT, gaiac-based faecal occult blood testing; OR, odds ratio; Se, sensitivity; Sp, specificity.

CRC screening strategies

Screening strategies were compared based on the observed participation rate of 29.1% in France. This rate was applied to the target population, that is, individuals aged 50–74, and does not include criteria excluding individuals from the national screening program. These mainly included individuals at higher risk, previous positive screening and history of colon adenoma. These exclusions are estimated to account for 13.2% of the target population in France. Thus, the observed participation rate used in the model (29.1%) translates to 33.6% of the eligible population after taking exclusion criteria into account. This participation rate was used for stool testing.[8] For blood-based screening, it was assumed that participation could be as high as 65%, as seen in France with PSA-based prostate cancer screening. A similar participation of 25% was assumed for colon capsule, colonoscopy and sigmoidoscopy.[30] It was assumed that CTC would have a similar participation rate to stool testing.

In the model, all individuals began screening at 50, stopping at age 74. The probability of participation at each screening cycle was varied stochastically between individuals based on previous participation, age and sex,[8,31,32] in order to better capture real-world participation structure. Individuals with a positive screening test (excluding the colonoscopy-only strategy) 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.[8] If negative, individuals did not undergo screening for the next 5 years for stool- and blood-based tests, or 10 years for the other tests, based on the current French program guidelines. Individuals with adenomas that were detected and removed were assumed to undergo colonoscopy monitoring as per French guidelines. Patients with low-risk polyps (fewer than three polyps found, no polyp larger than 10 mm and only low-grade dysplasia) are recommended to undergo a new colonoscopy after 5 years. Patients with high-risk polyps are recommended to undergo a new colonoscopy after 3 years. Patients with only low-grade initially and no polyps on the follow-up colonoscopy can delay the third colonoscopy by an additional 5 years (i.e. 10 years) and stop if the third colonoscopy is negative. Assumptions were made for the grade distribution for adenomas <10 mm.[34] It was assumed that monitoring continued until the diagnosis of CRC or 80 years. Compliance with the recommended follow up and monitoring was set to 31% based on data for high-risk patients in France.

Test characteristics

Test characteristics were based on literature review and are detailed in Table 2. For stool-based tests, we assumed that adenomas smaller than 10 mm were not detectable as true positives given that sensitivity and specificity are reported for advanced adenomas and CRC only.[15,35] A threshold of 30 µgHb/ml was used for the OC-Censor® test, as this is the threshold currently used in the French context. The study by Hoi *et al.*, comparing the performance of different thresholds for OC-Censor®, was used to extrapolate the specificity and sensitivity of OC-Censor® at that threshold.[36] Similarly, for blood-based tests, we assumed that only CRC was detectable.[16] For colonoscopy, colon capsule, CTC and sigmoidoscopy, sensitivity depended on the size of the adenoma,[24,28,37,38] with only colonoscopy and sigmoidoscopy able to detect adenomas smaller than 5 mm. It was assumed that sigmoidoscopy would have the same performance as colonoscopy but could detect only distal lesions. Patients undergoing colon capsule, CTC and colonoscopy were assumed to be at risk of serious complications (Table 2).[25,39] Adverse events resulting from colonoscopy, colon capsule and CTC were included in the model. Rates were different if colonoscopy was associated with a polypectomy. Rates of complications ranged from 1% for bleeding association with polypectomy to 3‰ for retention with CTC (Table 2).[25,39–41] Complications were associated with additional costs and disutilities.

Cost and utilities

Table 1 details the cost and utilities used in this study. The cost-effectiveness analysis included only direct medical cost valued from the societal perspective. 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 studies 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.[49] Fixed costs related to the screening program were not included as they were assumed to be similar across all screening strategies. CRC health status was associated with poorer utilities based on the literature.[26] Serious complications were associated with disutilities.[27]

Validation

The model results were compared with observed results of the national screening program with FIT and gFOBT for previous years. The model faithfully reproduces the positivity rates by sex and the positive predictive value of a positive FIT and gFOBT for advanced adenomas and CRC (supplemental file).

Cost-effectiveness analysis

Incremental cost-effectiveness ratios (ICERs) were calculated for quality-adjusted life-years (QALYs). Costs and QALYs were discounted

Table 2. Test performances.

Test		
gFOBT	Se: CRC 45.0% AA: 13.0% Sp: 97.8%	Hirai *et al.*, 2016[46] Launois *et al.*, 2014[47]
FIT	Se: CRC 75.0% AA: 30.0% Sp: 96.6%	Robertson 2017[34] adjusted with Hol *et al.*, 2009[48]
Stool DNA	Se: CRC 92.3% AA: 42.4% Sp: 86.6%	Imperiale *et al.*, 2014[15]
Blood-based	Se: CRC 66.0% Sp: 91.0%	Yan 2016[16]
Colonoscopy	Se: CRC: 95% >6 mm: 90% ⩽6 mm: 45% Sp: 95%	HAS 2010[6]
CTC	Se: CRC: 84% >10 mm: 76% ⩽6 mm: 44% Sp: 89%	HAS 2010[6] and Weinberg 2018[28]
Colon capsule	Se: CRC: 87% >10 mm: 86% ⩽6 mm: 87% Sp: 92%	HAS 2010[6] and Spada, 2016[24]
Sigmoidoscopy	Equal to colonoscopy for distal lesions only	Assumptions
Severe Complications		
Colonoscopy	No resection Bleeding: 0.06% Perforation: 0.04% Others: 0.04% Resection Bleeding: 0.98% Perforation: 0.08% Others: 0.10%	Denis 2013[38] Reumkens 2016[25]
Colon capsule	Retention: 0.03%	ESGE 2018[39]
CTC	Perforation: 0.04%	Bellini 2014[40]

AA, advanced adenoma; CRC, colon cancer; CTC, computed tomography colonography; FIT, faecal occult blood testing with immunoassay; gFOBT, gaiac-based faecal occult blood testing; OR, odds ratio; Se, sensitivity; Sp, specificity.

because the cost and the benefits of screening incur at different times.[29] We chose a 4% per year, according to French guidelines for cost-effectiveness studies.[42] A willingness-to-pay threshold of €40,000/QALY was used.

The robustness of the model was tested using deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). In DSA, results are produced by changing each parameter's value for the lower and upper bound of its 95% confidence intervals (or at ±20% of the baseline value when the confidence intervals were not available). In PSA, results are produced by a bootstrap process. Each iteration is based on changing the values of all parameters for a value randomly drawn within their 95% confidence intervals (or at ±20%). PSA results are based on the average of 500 iterations. Parameters' uncertainty and distribution are presented in the supplemental material. In addition, a scenario was tested with a theoretical participation rate of 100% for all scenarios for comparative purposes across the test technologies.

Results
In the French context, compared with FIT, every strategy, excluding gFOBT, was associated with a reduction in the cumulated lifetime incidence of

Table 3. Results.

Undiscounted results	FIT (Ref/1000 individuals)	gFOBT	Fecal DNA	Blood-based	Colonoscopy	Sigmoidoscopy	CTC	Colon capsule
CRC Incidence	44.22	+4.7%	−6.0%	+0.1%	−4.5%	−3.2%	−0.2%	−1.2%
CRC-related death	19.35	+8.4%	−7.0%	−15.6%	+2.9%	+4.3%	+6.7%	+6.5%
Adenomas <10 mm Screened	5.77	−36.6%	+215.3%	+371.8%	+401.3%	+255.7%	+20.9%	+18.6%
Adenomas ⩾10 mm Screened	21.34	−48.5%	+22.4%	−97.3%	−38.4%	−44.6%	−37.2%	−46.3%
CRC Screened	2.77	−28.0%	+5.4%	+161.7%	−73.0%	−76.8%	−69.4%	−76.2%
Screened Test undergone	2277	+1.2%	−5.7%	+149.2%	–	−80.2%	−75.3%	−80.1%
Colonoscopy Undergone	113	−36.6%	+199.0%	+345.5%	+354.6%	−5.5%	+16.7%	+14.3%
Undiscounted CRC-Related Cost (k€)	1018.72	+5.6%	−6.3%	−3.2%	−3.1%	−1.6%	+1.2%	+0.4%
Undiscounted Screening Cost (k€)	172.49	−26.7%	+394.0%	+589.8%	+178.2%	−11.9%	+11.6%	+115.5%
Undiscounted total cost (k€)	1191.21	+0.9%	+51.7%	+82.6%	+23.2%	−3.1%	+2.7%	+17.1%

CRC, Colon Cancer; CTC, Computed Tomography Colonography; FIT, fecal occult blood testing with immunoassay; gFOBT, gaiac-based fecal occult blood testing.

CRC (from 50 to death) between 0.2% for CTC to 6.0% for stool DNA testing. However, only two strategies, i.e. stool DNA testing (7.0%) and blood-based testing (15.6%), were associated with a reduction in CRC-related mortality (Table 3).

The other strategies were associated with a decrease in advanced adenoma and CRC detection compared with FIT. The apparent discrepancy with incidence results were related to the fact that CTC, colon capsule, colonoscopy and sigmoidoscopy were all associated with a significant increase in the detection of adenomas <10 mm (between 155.8% and 371.0%). This increase led to more patients leaving the screening program and undergoing colonoscopy monitoring every 3–5 years.

Furthermore, with the exception of sigmoidoscopy and gFOBT, all strategies were associated with an increase in the rate of severe adverse event related to the screening or treatment of adenomas compared with FIT. The increase was up to 340% for colonoscopy, 325% for blood-based testing and 195% for stool DNA testing (supplemental material) and were related mainly to the increase of colonoscopy performed either because of poor sensitivity or due to detection of small adenomas.

Only stool DNA testing was associated with an increase in the number of advanced lesions detected with screening compared with FIT (20.4%), including a 22.4% increase in advanced adenoma detection and a 5.4% increase in CRC. Blood-based testing was associated with an increase in CRC detection only (161.7%)

The FIT strategy was associated with an average of 2.28 FIT tests per individual between 50 and 74 years. On average, individuals underwent 0.11 colonoscopies, including screening confirmation and colonoscopy monitoring. CTC, colon capsule, and sigmoidoscopy were associated with a reduced number of screening tests performed due to the lower participation rate, and a longer

Table 4. Cost-effectiveness results.

Real-world participation rates								
CE results (*versus* no screening)	FIT	gFOBT	Fecal DNA	Blood-based	Colonoscopy	Sigmoidoscopy	CTC	Colon capsule
QALY (/1000)	14.0	7.3	14.1	16.9	9.8	8.7	7.2	8.2
Discounted Cost (€)	50.52	44.05	335.73	498.92	197.53	40.62	67.4	152.61
ICER (€/QALY)	3609	Dominated	Weakly Dominated	154,621	Dominated	Weakly Dominated	Dominated	Dominated
Theoretical 100% participation rates								
CE results (*versus* no screening)	Blood-based	gFOBT	CTC	FIT	Colon capsule	Fecal DNA	Sigmoidoscopy	Colonoscopy
QALY (/1000)	18.6	21.8	30.8	31.1	33.2	38	38.1	42.2
Discounted Cost (€)	623.41	101.58	235.26	118.7	671.64	1002.32	167.4	860.84
ICER (€/QALY)	Dominated	Weakly Dominated	Dominated	3817	Dominated	Dominated	6957	169,132

CRC, Colon Cancer; CTC, Computed Tomography Colonography; FIT, fecal occult blood testing with immunoassay; gFOBT, gaiac-based fecal occult blood testing; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

interval between screening cycles with between 0.56 and 0.45 tests per individual. The associated number of colonoscopies varied between 0.11 and 0.13 – roughly similar to FIT.

Compared with FIT, at a similar participation rate, stool DNA testing was associated with a 199.0% increase in colonoscopy. Blood-based testing was associated with 5.68 tests per individual on average, in line with its increase in participation with 0.50 colonoscopies.

The FIT strategy was associated with an average undiscounted cost of screening of €172 per individual between 50 and 74 years (Table 4), or €14 per screening cycle. The average undiscounted CRC-related cost with the FIT strategy was €1018 per individual. With the exception of gFOBT and sigmoidoscopy, every strategy was associated with an increase in screening cost from 11.6% (CTC) to 589.8% (blood-based testing). Colonoscopy only was associated with an increase of 178.2%. Due to the associated reduced incidence, most strategies were associated with a reduction in CRC-related cost that was not sufficient to offset the increase in screening cost. Overall, only the sigmoidoscopy strategy was associated with a lower total undiscounted cost compared with FIT.

For discounted QALY and cost, compared with no screening, FIT was associated with an increase of 14.0 QALY for a €50,520 per 1000 individuals, or an ICER of €3600/QALY. Only stool DNA and blood-based testing were associated with an increase in QALY compared with FIT with 0.10 QALY and 2.90 QALY per 1000 individuals, respectively. Thus, as most strategies were associated with higher discounted costs, only stool DNA and blood-based testing were not strongly dominated by the FIT strategy. However, stool DNA testing was weakly dominated by blood-based testing. The ICER associated with blood-based testing was €154,600/QALY.

Sensitivity analysis
Sensitivity analysis results are shown in Figure 2. DSA results show that the parameters most
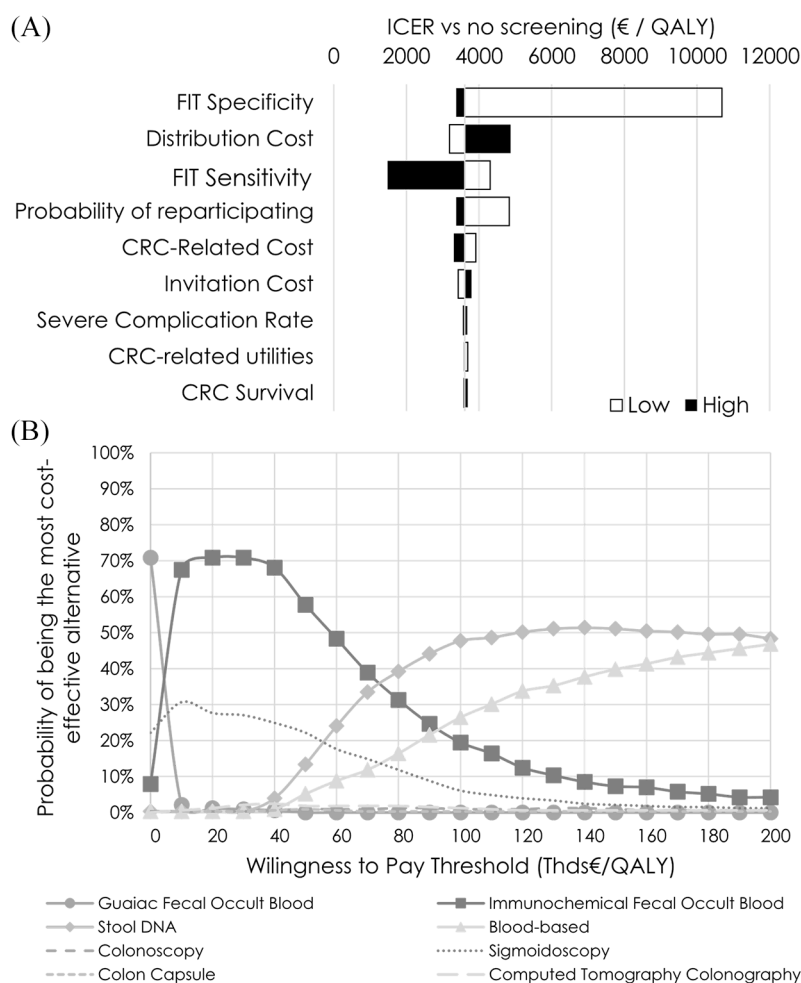
Figure 2. Sensitivity analysis results. (A) Parameters most affecting the ICER of FIT assessed by DSA. (B) PSA of cost-effectiveness versus willingness-to-pay threshold.
DSA, deterministic sensitivity analysis; FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

affecting the ICER of FIT are specificity (ICER of €10,500/QALY with the lower bound of FIT specificity of 91.2%), sensitivity (ICER of €1800/QALY with the higher bound of FIT sensitivity of 78.8%). For all other parameters, the ICER remained in the €3000/QALY–€5000/QALY range.

PSA shows the probability of a given scenario to be the most cost effective at varying willingness to pay threshold when taking into account parameters uncertainty. It confirms the robustness of the results, with FIT being the most cost-effective alternatives for a willingness-to-pay threshold between €4000/QALY and €75,000/QALY.

When considering a participation rate of 100% for all scenarios, FIT remained a very cost-effective

alternative with an ICER under €4000/QALY. Sigmoidoscopy went for being weakly dominated to being associated with an ICER of €7000/QALY and was the second most effective screening strategy. Colonoscopy became the most effective strategy, with a 25% increase in QALY gains compared with FIT but was associated with an ICER of €170,000/QALY because of the high cost of the procedure. All other strategies were dominated by sigmoidoscopy (Table 4).

Discussion

In the French context, given the current participation rate of 29.1%, the current screening strategy based on FIT (30 µg/ml) every 2 years between 50 and 74 years appears to be the most cost-effective

alternative, dominating most of the other strategies. Looking only at gFOBT, FIT and colonoscopy, these results are in line with results reported from previous publications that showed that biannual FIT was more cost-effective that gFOBT, and that FIT was either cost-saving or very cost-effective compared with colonoscopy every 10 years.[9–14] However, these results extend these conclusions to show that FIT is also more cost-effective than newer alternatives including CTC, 2nd generation colon capsule, stool DNA or blood-based when considering a willingness to pay threshold of €40,000/QALY.

In addition, the ICER of €4000/QALY associated with FIT *versus* no screening, suggests, despite European and French guidelines, that screening is cost-effective even at participation rates under 45%.

In this analysis, strategies based on colonoscopy, CTC, colon capsule, and sigmoidoscopy every 10 years are associated with lower QALY, despite being associated with a reduction in the incidence. This seemingly counterintuitive result is likely due to two factors. First, they tend to screen fewer patients as they are undergone at longer intervals with a lower participation rate, greatly reducing the potential effectiveness of the screening strategy. Second, they compensate by having increased sensitivity compared with FIT and being able to detect small adenomas leading to more individuals with adenomas being referred for follow up by colonoscopy; hence, the reduction in CRC incidence. However, this leads to a very different impact of screening from stool-based strategies. The results show that, overall, colonoscopy, CTC, colon capsule, and sigmoidoscopy tend to identify patients earlier in the adenoma-carcinoma sequence, with 4 times as many adenomas <10 mm diagnosed. This leads to a large number of patients with a history of adenoma being followed up at 3- to 5-year intervals. However, they tend to identify fewer adenomas ≥10 mm or CRCs, as their prevalence is lower in the population, limiting the impact of cancer-screening stage-shift and thus ultimately in respect of CRC mortality and QALY.[43–45] It is important to note that this conclusion is based on low participation rates, and that the conclusion is different with perfect participation. Indeed, with 100% participation, colonoscopy and sigmoidoscopy are the most effective alternatives because of their high sensitivity, and sigmoidoscopy becomes a cost-effective strategy.

In addition, the increase in colonoscopies and the higher cost of the tests leads to an increase in screening costs of up to 4-fold. Thus, these strategies were either dominated or associated with ICER over €150,000/QALY, and thus considered to be inefficient. Importantly, this increase in costs reflects only the cost of performing the screening tests and does not take into account the significant infrastructure investments that would be needed. Indeed, currently available colonoscopy resources would be insufficient for the large increase in colonoscopies needed. Large investment in colonoscopes and training would be required, increasing the overall cost differences compared with FIT.

The analysis also included the newer stool-DNA testing that is associated with higher sensitivity than FIT at the cost of lower specificity. This test appears to be promising as it was the only alternative associated with a reduction in the CRC incidence and prevalence compared with FIT. However, this reduction was associated with a 3-fold increase in colonoscopies performed and thus serious adverse events, in part because of the increase in the number of false positives. This would place a significant burden on the healthcare system and increase the morbidity of colonoscopy-related adverse events. Similarly, blood-based testing (mSEPT9 marker) was also associated with an ICER of over €150,000. Surprisingly, despite not being able to detect adenomas, it was not associated with an increase in incidence. Indeed, low specificity combined with high participation rate led to a very large number of patients undergoing colonoscopy (7-fold increase), which would be incompatible with current French healthcare system capacity.

Both blood-based and stool-DNA testing are characterized by high sensitivity and low specificity. Although, high sensitivity is often considered a desirable attribute of a test, it might not be the case for CRC screening in the general population. First, the low prevalence leads to a low positive predictive value when the specificity is low. It means that most individuals who test positive will not have adenomas or CRC, which leads to mostly unnecessary colonoscopy. Second, the slow progression of adenomas means that screening can be based on multiple rounds without significantly reducing its efficacy. Sensitivity increases exponentially with each additional round even though sensitivity for each round is

low. Thus, in this context, a high specificity test with a good sensitivity might be more desirable than a high sensitivity test. Blood-based and stool-DNA testing might be more suited to context where both the prevalence is high and risk of interval cancer is high, such as in high-risk individuals.

The sensitivity analysis for FIT showed that specificity is a key parameter for the ICER, and improvement in specificity, as well as a reduction in cost would be required for the stool-DNA testing being associated with a lower ICER.

These results were obtained using a simulation model based on previously published assumptions.[18] Moreover, the model has been calibrated and validated on French epidemiological data. This reinforces confidence in its validity.

The main limitations are related to the uncertainty around the performance parameters of the different tests although the sensitivity analyses carried out, taking this uncertainty into account, show results that are consistent with the reference analysis. This is especially true for stool DNA and blood testing that have only limited evidence and have never been evaluated in large-scale screening programs. They were, nevertheless, included to provide some insights into their potential role if their performances were to be confirmed.

Furthermore, 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.[50] The impact of not including serrated adenomas is difficult to assess in the absence of data; additional studies are necessary. The weight of serrated adenomas in interval cancers,[26,39,50–54] and their more difficult detection with colonoscopy,[20,28,54,55] may 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.[5,19,56,57]

Finally, the results are sensitive to the choice of participation rates for each test. We used real-world data for stool testing from the current screening program, but other tests are based on assumptions. We used conservative participation rates for colonoscopy and sigmoidoscopy, and it is unlikely that they would be associated with higher or similar rates than FIT given the high burden associated with undergoing these examinations. Our findings may need to be reviewed if participation rates rose to the range of 75 percent or over.

In conclusion, our results suggest that, at a real-world participation rate of 29.1%, CRC screening based on FIT is one of the most effective, and the most cost-effective, alternative. Efficient and effective gains could not be obtained by switching FIT-based screening to a colonoscopy-based screening or more sensitive tests such as blood-based or faecal DNA testing. In the absence of a more effective testing strategy, these results support that an increase in screening participation would be the main strategy to increase the efficacy of CRC screening and further reduce CRC incidence and mortality.

Conflict of interest statement
S Barré, H Leleu, A Vimont, S Taleb, JC Saurin and F De Bels declare no conflict of interest. R Benamouzig has received honoraria from Alfasigm, Bayer, Medtronic and Mayoli.

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

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.

ORCID iD

Henri Leleu (iD) https://orcid.org/0000-0003-4930-6767

Supplemental material

Supplemental material for this article is available online.

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