Cost-utility analysis of real-time artificial intelligence-assisted colonoscopy in Italy

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ABSTRACT

Background and study aims Artificial intelligence (AI)-assisted colonoscopy has proven to be effective compared with colonoscopy alone in an average-risk population. We aimed to evaluate the cost-utility of GI GENIUS, the first marketed real-time AI system in an Italian high-risk population.

Methods A 1-year cycle cohort Markov model was developed to simulate the disease evolution of a cohort of Italian individuals positive on fecal immunochemical test (FIT), aged 50 years, undergoing colonoscopy with or without the AI system. Adenoma or colorectal cancer (CRC) were identified according to detection rates specific for each technique. Costs were estimated from the Italian National Health Service perspective.

Results Colonoscopy + AI system was dominant with respect to standard colonoscopy. The GI GENIUS system prevented 155 CRC cases (–2.7%), 77 CRC-related deaths (–2.8%), and improved quality of life (+0.027 QALY) with respect to colonoscopy alone. The increase in screening cost (+€10.50) and care for adenoma (+€3.53) was offset by the savings in cost of care for CRC (–€28.37), leading to a total savings of €14.34 per patient. Probabilistic sensitivity analysis confirmed the cost-efficacy of the AI system (almost 80% probability).

Conclusions The implementation of AI detection tools in colonoscopy after patients test FIT-positive seems to be a cost-saving strategy for preventing CRC incidence and mortality.

Introduction

Globally, 1.8 million colorectal cancer (CRC) cases and 881,000 deaths were estimated for 2018 [1]. In Italy, CRC is the second leading cause of oncological death, preceded by lung cancer in males and breast cancer in females [2].

Screening programs are particularly useful as the progression of the disease is typically slow, generally taking several years or even a decade [3]. In Italy, most CRC screening programs provide the fecal immunochemical test (FIT) offered every 2 years to a range of populations that varies from 50- to 74-year-old citizens, according to the region [4]. In case of FIT positivity, total colonoscopy is performed as a second-level diagnostic test. Great differences may be observed among northern, central, and southern areas in Italy both concerning the

target populations and the participation rate [4]. Screening programs have proven to be effective as mortality reduction for CRC was observed utilizing FIT (41%), flexible sigmoidoscopy (21%-30%), and colonoscopy (88%) screening tests [5].

Despite the efficiency of screening programs, a worrying lesion miss rate still afflicts many colonoscopies. A 26%, 9%, and 27% miss rate were calculated for adenomas, advanced adenomas, and serrated polyps, respectively, after colonoscopy [6]. Adenoma miss rates vary greatly, from 17% to 48%, based on the ability of the endoscopist [7].

Recently developed artificial intelligence (AI) software tools aim at guiding endoscopists to identify polyps during colonoscopy by real-time pattern recognition, similar to a face-recognition application [8]. Briefly, they come as AI-based devices which, after proper training, are able to perform real-time automatic detection of polyps. The first marketed real-time computer-aided detection (CADe) system to be added to endoscopic equipment during colonoscopy is GI GENIUS Intelligent Endoscopy Module (Medtronic, Dublin, Ireland), which from now on will be mentioned also as CADe. This AI system is able to highlight with green squares in real-time the regions that have visual characteristics consistent with different types of mucosal abnormalities, thus aiding clinicians, who independently assess potential lesions and subsequently take appropriate actions [9]. As has been demonstrated in several clinical studies, the use of CADe increases adenoma detection rate (ADR) and the number of adenomas per colonoscopy (APC), irrespective of adenoma size [8, 10].

As mentioned, AI-assisted colonoscopy with CADe proved to be effective compared with colonoscopy alone in a parallel randomized multicenter trial [10] enrolling 40- to 80-year-old patients undergoing colonoscopy due to primary CRC screening, post-polypectomy surveillance, FIT positivity, or signs and symptoms. Among 341 patients in the AI arm, a 30% and 46% relative increase in ADR and APC, respectively, were observed in comparison with 344 patients undergoing colonoscopy without computer-aided polyp detection, regardless of morphology or location.

In this study, we aimed to analyze the cost-effectiveness of CADe-assisted colonoscopy in the detection of adenomas and colorectal cancer in Italy.

Methods

Model overview

A 1-year cycle cohort Markov model was developed in MS Excel to evaluate the cost-utility of high-definition colonoscopy with or without an AI system in Italian FIT-positive patients. The simulated cohort consisted of 100,000 hypothetical patients aged 50 undergoing colonoscopy after positive FIT results and followed until death (life time horizon of 70 years). Data used to populate the model are shown in ▶ Table 1, whereas the model structure is illustrated in ▶ Fig. 1. Adenomas (small, medium, or large) or CRC are identified according to detection rates, which are specific for each technique, i.e., colonoscopy alone or colonoscopy + AI system. The model assumes no false-negatives in

▶ Table 1 Input parameters.

Variable	Base case	SE or 95% CI	Distribution	Reference
Sex (% male)	46.6%	10% base case	Lognormal*	[11]
FIT-positive starting patients				
• Healthy	40.4%		Dirichlet	[4][6][11][12]
• Small adenoma	34.0%			
• Medium adenoma	10.6%			
• Large adenoma	10.4%			
• CRC I	2.4%			
• CRC II	0.9%			
• CRC III	1.2%			
• FIT-positive rate	4.1%	10% base case	Lognormal*	[11]
AMR				
• Small adenoma	31%	25 to 38%	Lognormal*	[6]
• Medium adenoma	19%	12 to 28%	Lognormal*	[6]
• Large adenoma	9%	4 to 16%	Lognormal*	[6]
• CRC stage I-II†	4.5%	2 to 8%	Lognormal*	Assumption
IRR APC (with vs without GI GENIUS)				
• Small-to-medium adenoma	1.50	1.17 to 1.91	Lognormal	[10]
• Large adenoma	1.07	10% base case	Lognormal	[10]

▶ Table 1 (Continuation)

| Variable	Base case	SE or 95% CI	Distribution	Reference
▪ CRC	3.36	0.93 to 12.11	Lognormal	[10]
Transition probabilities				
▪ Healthy-to-small adenoma (age 50)	0.8%	0.4 to 1.7%	Lognormal*	[13]
▪ Healthy-to-small adenoma (age 55)	1.0%	0.5 to 2%	Lognormal*	[13]
▪ Healthy-to-small adenoma (age 60)	1.2%	0.6 to 2.3%	Lognormal*	[13]
▪ Healthy-to-small adenoma (age 65)	1.3%	0.7 to 2.7%	Lognormal*	[13]
▪ Healthy-to-small adenoma (age 70)	1.5%	0.8 to 3%	Lognormal*	[13]
▪ Small-to-medium adenoma	3.5%	1.7 to 6.9%	Lognormal*	[13]
▪ Medium-to-large adenoma	2.2%	1.1 to 4.3%	Lognormal*	[13]
▪ Large adenoma to CRC I	37.0%	26.8 to 47.2%	Lognormal*	[13]
▪ CRC I to II	23.8%	20.6 to 27.1%	Lognormal*	[13]
▪ CRC II to III	48.5%	32.1 to 65%	Lognormal*	[13]
▪ CRC III to IV	30.2%	15.1 to 60.4%	Lognormal*	[13]
Recurrence risk post-surgery				
▪ CRC I-II	5.7%	10% base case	Lognormal*	[14]
▪ CRC III-IV	17.5%	10% base case	Lognormal*	[14]
Costs				
▪ FIT	€ 3.52	10% base case	Normal	[15]
▪ Colonoscopy	€ 86.80	10% base case	Normal	[15]
▪ GI GENIUS per colonoscopy	€ 9.67	10% base case	Normal	Assumption
▪ Endoscopic polypectomy	€ 116.16	10% base case	Normal	[15]
▪ CRC surgery	€ 7,253.09	10% base case	Normal	[15][16]
▪ Adjuvant chemotherapy	€ 9,612.91	10% base case	Normal	[15]
▪ Systemic chemotherapy	€ 13,760.39	10% base case	Normal	[17]
▪ Postsurgical FU adenoma and CRC I	€ 306.00	10% base case	Normal	[15]
▪ Postsurgical FU CRC II-III	€ 1,377.65	10% base case	Normal	[15]
Utilities				
▪ Adenoma	0.91	0.87 to 0.93	Lognormal*	[13]
▪ CRC I-II	0.67	0.62 to 0.72	Lognormal*	[13]
▪ CRC III	0.59	0.54 to 0.69	Lognormal*	[13]
▪ CRC IV	0.25	0.2 to 0.31	Lognormal*	[13]

AMR, adenoma missing rate; APC, adenomas per colonoscopy; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; FU, follow-up; IRR, incidence rate ratio.
*Each probability p was transformed into an odds according to the formula p/(1-p) and the resulting odds was sampled from a lognormal distribution.
†Assumed 50% of large adenoma AMR.

case of CRC stage III-IV or CRC recurrences due to symptoms or more comprehensive monitoring. Undetected patients (i.e., false-negatives) are considered healthy, follow-up FIT is scheduled after 5 years and disease progression is simulated. Conversely, CRC-detected patients undergo surgery and eventually chemotherapy. After 1 year of follow-up, patients treated for adenoma are considered cured and the next examination is scheduled depending on risk level: FIT after 5 years for low-risk patients (small-medium adenoma) or colonoscopy after 3 years for high-risk patients (large adenoma). Patients treated for CRC move into a post-treatment state where they can experience
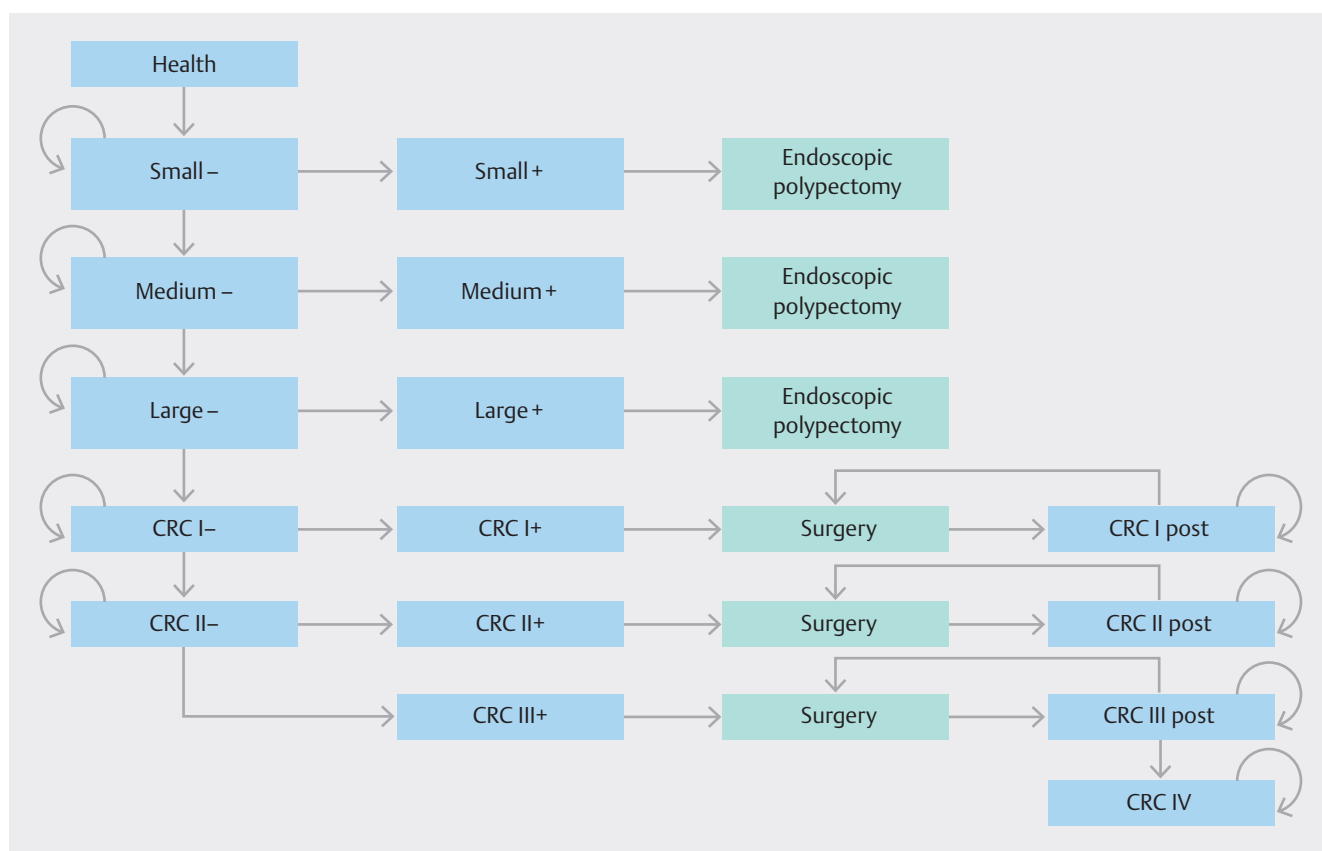
▶ **Fig. 1** Markov model structure. CRC, colorectal cancer; symbol "-" and "+" mean undiagnosed and diagnosed, respectively.

recurrences associated with worsened outcomes (e. g., higher mortality).

The natural history model (no colonoscopy after FIT-positive result) was validated by comparing the predicted CRC incidence and mortality with those observed in two previous studies on FIT-positive patients without follow-up colonoscopy examination [18] or with a delayed follow-up colonoscopy examination [19]. The no-colonoscopy scenario was simulated only to validate the simulation model, it was not included in the cost-effectiveness analysis because the diagnostic follow-up is recommended by international guidelines in case of FIT-positive patients.

Costs were expressed in euros (€) and updated to 2021 according to Harmonized Indices of Consumer Prices specific for the Italian Health Sector [20]. Both costs and consequences of the two alternatives were discounted at an annual rate of 3.5% in the base case scenario, with sensitivity analyses ranging between 0 and 5%.

Clinical data

Prevalence of adenomas or CRC was estimated from the results of five screening programs conducted in the Veneto region between 2002 and 2015 [11]. Among 18,179 FIT-positive patients, 7,557 (41.6%) were diagnosed with advanced or non-advanced adenoma and 781 (4.3%) were diagnosed with CRC. Prevalence of adenomas was categorized into small (≤5 mm),

medium (6–9 mm), and large (≥10 mm) according to detection frequency observed in 72,021 colonoscopies performed for FIT-positive patients in the EQuIPE study [12] (56.4% small, 20.7% medium, and 22.8% large). CRC prevalence was divided according to the stage at diagnosis of 3,733 cases screen-detected by 104 FIT programs from 2011 to 2012 in Italy [4] (52.7% stage I, 20.0% stage II, and 27.3% stage III-IV). In addition, estimated prevalence was adjusted for adenoma miss rate (AMR) from the meta-analysis of Zhao et al. 2019 [6], to take into account the false-negatives from colonoscopy and to calculate the "real" prevalence of adenomas or CRC.

The probability of detecting adenomas or CRC correctly with colonoscopy (i. e. the sensitivity) was estimated as 1 minus the AMR from Zhao et al. 2019 [6], assuming a CRC miss rate equal to 50% of AMR. The sensitivity of colonoscopy + AI was then estimated by applying the incidence rate ratio (IRR) for APC estimated in the CADe system randomized controlled trial [10] to the sensitivity of colonoscopy alone. IRR APC-specific for CRC was not available; therefore, as a proxy, we used the relative risk (RR) of detection rate per patient.

Natural disease evolution was simulated according to annual transition probabilities used in the previous cost-effectiveness analysis of Coretti et al. [13]. The risk of recurrence after CRC treatment was stage-specific (5.7% for stage I-II and 17.5% for stage III-IV) according to the digestive cancer registries of two French administrative areas [14]. Finally, 2019 general popula-
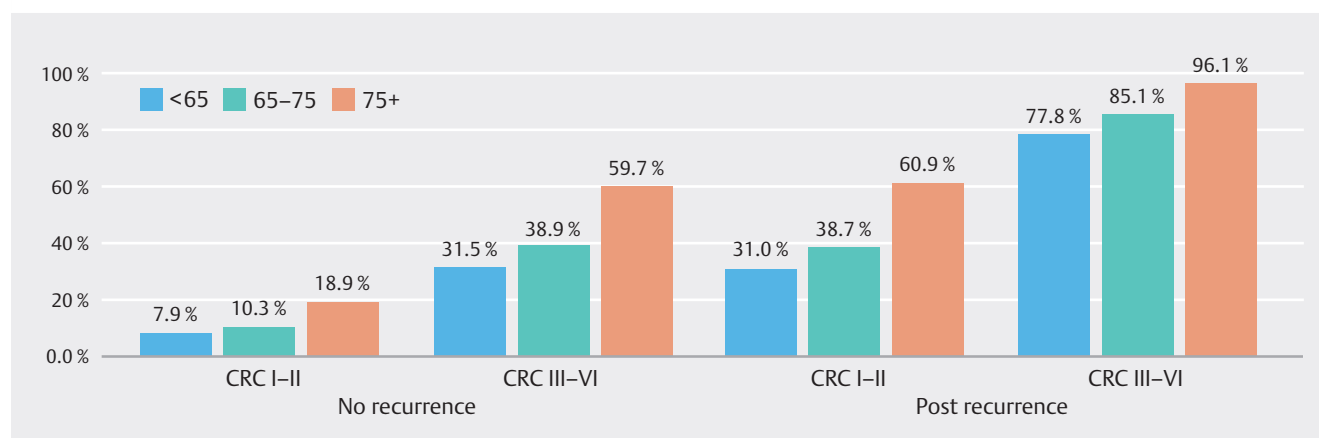
▶Fig. 2 Annual mortality for CRC patients. CRC, colorectal cancer. Mortality risks by age class (65–75 and ≥ 75) and recurrence were estimated from mortality risk age class ≤ 65 using hazard ratios from Gilard-Pioc et al.: $HR_{65-75\,vs.\,\leq 65} = 1.32$, $HR_{\geq 75\,vs.\,\leq 65} = 2.55$, $HR_{recurrence\,vs.\,no\,recurrence} = 4.54$.

tion mortality adjusted by age and gender was applied in every cycle of the model for patients with adenoma (https://demo.istat.it/); annual mortality for CRC patients (▶Fig. 2) was estimated from the 5-year CRC survival from the Surveillance Epidemiology and End Results program (SEER) 2000–2010 [18] specific for CRC stage, adjusted by age class and recurrence using hazard ratios from Gilard-Pioc et al. [14].

Efficacy was evaluated in terms of CRC prevention and mortality reduction by detection of CRC in earlier stages of the disease with better survival rates.

Cost data

Costs were estimated from the Italian National Health Service perspective, considering diagnostic procedures (FIT, colonoscopy with or without AI), colonoscopy with polypectomy in case of adenoma, and the cost of CRC treatments, such as surgery and/or chemotherapy.

Outpatient tariffs were used to estimate the cost per person of FIT (code 90.21.4), colonoscopy (code 45.23), and polypectomy in case of adenoma (endoscopic polypectomy code 45.42) [15]. The cost of CADe system allocated to each procedure was estimated considering an average cost of €43,500 for each GI GENIUS Intelligent Endoscopy Module purchased including 3 years of software upgrades and support, and assuming 1,500 colonoscopies performed annually (lower number of procedures were considered in a scenario analysis). The cost of surgery in case of CRC stages I-III was quantified by the weighted mean of National diagnosis-related groups (DRG) tariffs [15, 16]: 75.4% major intestine interventions (DRG 149), 11.7% rectal resection without complications (DRG 147), 6.1% rectal resection with complications (DRG 146), 5.1% minor intestine interventions without complications (DRG 153), and 1.6% minor intestine interventions with complications (DRG 152). Follow-up costs in the year post-surgery (or post-chemotherapy for CRC IV) included two abdominal instrumental exams (code 88.75.1) and four blood tests (code 90.81.5); in case of CRC II-IV, it was also assumed one positron emission tomography (code 92.18.6). Adjuvant treatment after CRC III surgery was

quantified assuming that the drugs used in chemotherapy were included in the DRG 410 reimbursed for chemotherapy. For systemic chemotherapy in case of CRC IV, it was assumed that 23.4% of patients were also treated with bevacizumab add-on therapy [17]. For both adjuvant and systemic chemotherapy, the model assumed 5.4 cycles per year on average [13].

Utility data

General population utilities adjusted by age and gender were used for healthy patients [21], while utilities specific for adenoma, CRC stage I-II, stage III, and stage IV (▶Table 1) were used according to a previous cost-effectiveness model developed for Italy [13].

Cost-utility analysis

The study results were expressed in terms of incremental cost-utility ratio (ICUR) between the screening strategy with CADe versus standard colonoscopy. Incremental costs were included in the numerator and incremental effectiveness in the denominator, in terms of quality-adjusted life-years (QALY), calculated by multiplying survival for utility weights specific for each health condition. The willingness to pay (WTP) was set at €57,234 per QALY, equal to twice the 2019 Italian gross domestic product (GDP) per capita, according to the WHO-CHOICE definition [22]. An intervention yielding a healthy year of life for less than three times GDP per capita was considered "cost-effective" and an intervention yielding a healthy year of life for less than one times GDP per capita was considered "very cost-effective". Moreover, an intervention yielding a healthy year of life without increasing the overall cost was called "dominant". This is the ideal scenario as the new intervention produces a better patient outcome at a reduced overall cost.

Sensitivity analyses and alternative scenario

A one-way deterministic sensitivity analysis (DSA) was conducted to identify the effect of uncertainty with input parameters on the cost-utility results. Baseline characteristics, AMR, AI effi-

cacy, utilities, and costs were varied between lower and upper limits of 95% confidence interval (CI), if available, or ± 20% of the base case (one by one, while all other variables are held at baseline values, i.e., stable). In addition, a multivariate probabilistic sensitivity analysis (PSA) was run to determine the effect of simultaneous variation of model parameters on the ICUR. Normal family distributions were chosen for almost all parameters (lognormal for IRRs, RRs, and odds-transformed probabilities, normal for utilities and cost), consistent with their use in the model as cohort means; transition probabilities were sampled from Dirichlet distributions. One thousand Monte Carlo simulations were generated to assess the distribution of these possible scenarios around the base case estimate. For each distribution, the mean value was the value used in the base case, the standard error was calculated from 95% confidence interval, if available, or was assumed equal to 10% of the mean as commonly used for sensitivity analyses (▶**Table 1**).

An alternative scenario was developed considering a more heterogenous population including also patients undergoing direct colonoscopy without previous FIT in order to evaluate the impact of AI in real-world practice. In this case, the adenoma and CRC "real" prevalence was estimated using the control arm of the AID-2 study [23] including 330 patients aged 40 to 80 years old, undergoing colonoscopy for colorectal neoplasia diagnosis. Indications for colonoscopy were: FIT-positive (7.3%), primary CRC screening (28.5%), surveillance (35.7%), and gastrointestinal symptoms (28.5%). Adenoma and CRC cases were adjusted for the same AMR used in the base case to estimate the real distribution of adenomas and CRC in this population. The resulting "real-word practice" cohort consisted of 40.0% healthy patients, 41.3% small adenoma, 9.7% medium adenoma, 8.0% large adenoma, and 1% CRC I (all CRC cases were assumed stage I, conservatively, as no information was available in the AID-2 study).

The base case was also evaluated after substituting in US Medicare National Average costs for 2021, to compare the economic impact of the CADe system with different healthcare system costs (**Table S1** and **Table S2** in Supplementary Material). All clinical parameters used in the base case were held constant in the US cost analysis, with only the unit costs changed.

Results

Base case scenario

Efficacy

In the no-colonoscopy simulation, 8,602 CRC cases and 4,613 CRC-related deaths per 100,000 people were estimated in the lifetime horizon of the simulation, corresponding to 86 CRC cases and 46 CRC-related deaths per 1,000 patients, respectively.

The simulation of colonoscopy in a cohort of 100,000 FIT-positive 50-year-old individuals (base case scenario) showed that the addition of CADe to the equipment allowed real-time detection of adenomas that resulted in a lower number of cases developing into an overt CRC (n = 5,579) with respect to those who underwent colonoscopy alone (n = 5,734), thus resulting

▶ **Table 2** Effect, cost, and net benefit for a cohort of 100,000 subjects undergone standard colonoscopy or colonoscopy + GI GENIUS: base case results (FIT-positive patients).

|	Standard colonoscopy	Colonoscopy + GI GENIUS system
CRC cases	5,734	5,579
CRC prevented (95% CI)	–	155 (–223 to 513)*
% CRC prevented (95% CI)	–	2.7% (–4.4 to 12.1)*
CRC deaths	2,763	2,686
CRC deaths prevented (95% CI)	–	77 (–95 to 239)*
% CRC deaths prevented (95% CI)	–	2.8% (–4.1 to 11.8)*
Life-years gained (95% CI)	–	2,373 years (–2,655 to 7,206)*
Gain in quality of life per person (95% CI)	–	0.027 QALY (–0.04 to 0.10)†
Total cost (per person)	€1,353.75	€1,339.41
Screening cost (per person)	€101.25	€111.75
Cost of care for adenoma (per person)	€150.32	€153.85
Cost of care for CRC (per person)	€1,102.18	€1,073.80
Total savings (per person) (95% CI)	–	€14.34 (–46.27 to 73.22)†
ICUR vs standard colonoscopy (incremental cost per QALY gained)	–	Dominant

CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; ICUR, incremental cost-utility ratio; QALY, quality-adjusted life-years.
*Colonoscopy + GI GENIUS system was more effective than standard colonoscopy in more than 80% of simulations.
†Colonoscopy + GI GENIUS system was more cost-effective than standard colonoscopy in more than 70% of simulations.

in a 2.7% reduction of CRC cases (–155 cases) (▶**Table 2**). A similar reduction rate (2.8%) was obtained in the number of prevented deaths (n = 77) as 2,686 CRC-related deaths were estimated in the cohort who underwent AI-assisted colonoscopy while 2,763 CRC-related deaths were estimated in the cohort undergoing colonoscopy alone (▶**Table 2**). In addition, the strategy of CADe-assisted colonoscopy resulted in 2,373 life-years gained and an observed gain in the quality of life (+ 0.027 QALY per person) (▶**Table 2**).
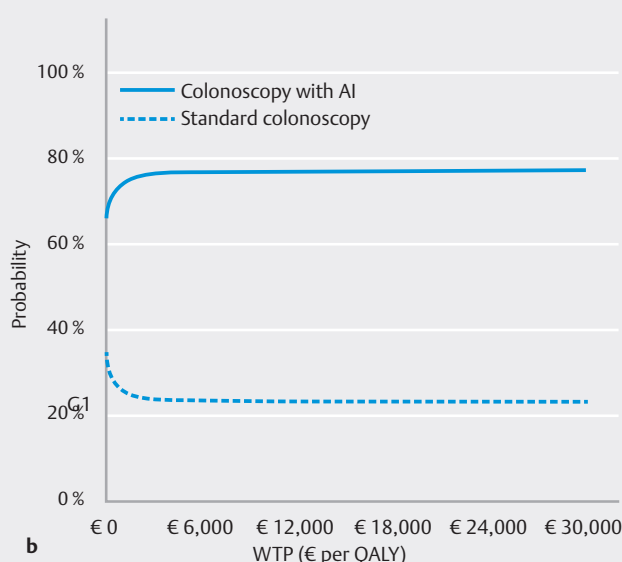
Costs

Compared to standard colonoscopy, AI-assisted colonoscopy was associated with higher costs per person for screening (€ 111.75 vs. €101.25, mean difference = +€10.50) and care for adenoma (€ 153.85 vs. €150.32, mean difference = +€3.53) but lower costs of care for CRC (€1,073.80 vs. 1,102.18, mean
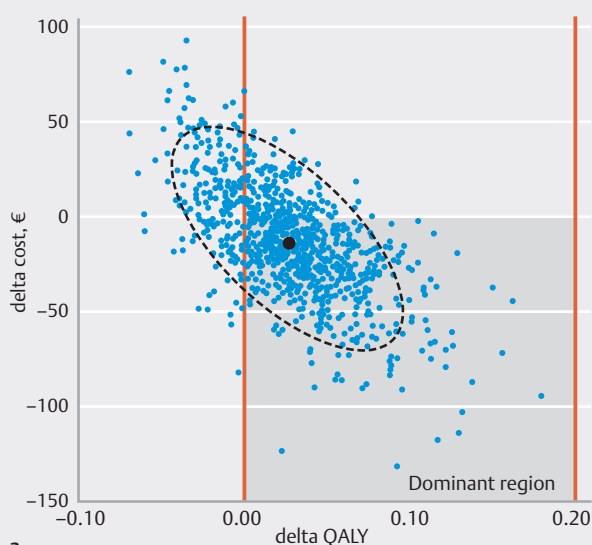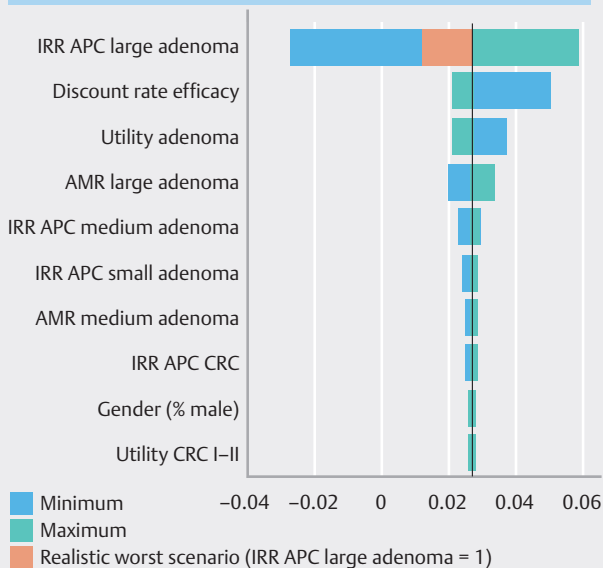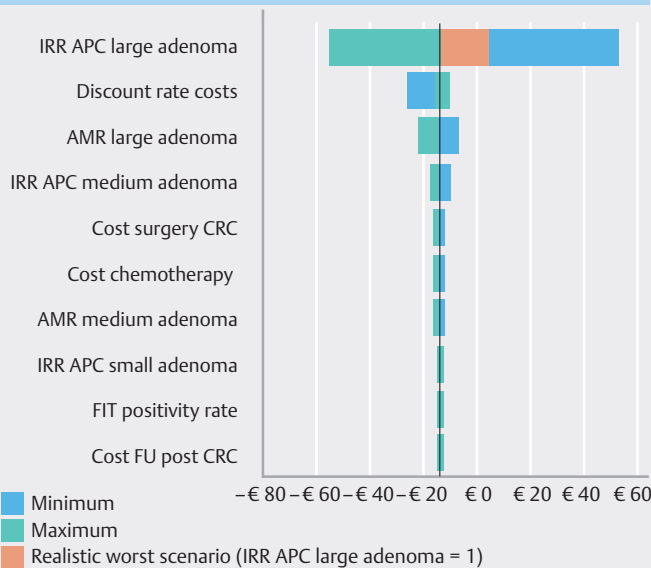
Fig. 3 Sensitivity analyses. AI, artificial intelligence; AMR, adenoma missing rate; APC, adenoma per colonoscopy; C/U, cost-utility; CRC, colorectal cancer; FIT, fecal immunochemical test; IRR, incidence rate ratio; QALY, quality-adjusted life-years; WTP, willingness to pay. The dominant region in gray (▶ Fig. 3a) represents results with better outcomes delivered with a lower cost (75% of simulations).

difference = −€28.37) (▶ Table 2). This resulted in an overall €14.34 total savings per person (▶ Table 2).

Cost-effectiveness

In the base case, the strategy of GI GENIUS-assisted colonoscopy was dominant with respect to standard colonoscopy (▶ Table 2) due to an improvement in both survival (+0.024 LY) and quality of life (+0.027 QALY) combined with a savings of €14.34 per patient undergoing AI-assisted colonoscopy post-

FIT-positive. When estimates of US healthcare system costs were input into the Markov model, the strategy of AI-assisted colonoscopy was also dominant with a savings of $20.16 per patient (**Supplementary Table S2**).

PSA confirmed base case results (▶ Fig. 3a) and despite the amount of uncertainty of input parameters (represented by the cloud around the base case), most of the confidence ellipse was located in the upper-left and the lower-right quadrants, indicating cost-effectiveness or dominant results. AI had an ap-

proximate 66% probability to be dominant with respect to standard colonoscopy (more effective and less costly) and the probability to be cost-effective was almost 80% for all WTP thresholds considered (▶ **Fig. 3b**).

According to DSA analysis, even more conservative assumptions on almost all parameters did not change the benefit in QALY and the savings (▶ **Fig. 3c**). The IRR of large APC was the only parameter that highly influenced the results: In fact, in the worst-case scenario, the parameter resulted in favor of colonoscopy alone (IRR = 0.86). However, it seems quite unrealistic to assume that CADe would reduce the sensitivity with respect to colonoscopy alone; in a more realistic scenario, simulating no benefit of AI on the detection of large adenomas (i. e., IRR = 1), the strategy was confirmed to be cost-effective with respect to standard colonoscopy with a negligible ICUR of € 340 per QALY gained (▶ **Fig. 3d**).

Alternative scenarios

CADe-assisted colonoscopy was dominant with respect to standard colonoscopy also in the "real-word practice" cohort of 100,000 62.6-year-old individuals, 47.3% male (▶ **Table 3**). The addition of AI to the equipment prevented 134 CRC cases, 56 CRC-related deaths, and improved quality of life (+ 0.010 QALY) with a total savings of €4.91 per person (▶ **Table 3**).

Scenario analysis on the number of colonoscopies per year highlighted that CADe-assisted colonoscopy was dominant with respect to standard colonoscopy up to 600 colonoscopies per year (**Fig. S1**). For more extreme scenarios (<600 colonoscopies per years), CADe-assisted colonoscopy was cost-effective with respect to standard colonoscopy with an ICUR lower than €5,000 per QALY gained (**Fig. S1**)

Discussion

In a simulation model, implementation of AI-assisted colonoscopy in the setting of a population-based organized FIT-positive CRC screening program appeared to result in cost savings. The efficacy of this intervention is primarily due to the CRC treatment costs averted due to a higher degree of cancer prevention enabled by a higher detection rate of precancerous neoplasia with AI-assisted FIT + -colonoscopy [18].

The primary explanation for the cost-saving profile of AI intervention – despite its additional cost – is related to its relatively high degree of efficacy. It could be argued that a mere 2.7% relative increase in CRC incidence (2.8% for mortality) prevention rate is apparently marginal as compared with an initial 10% increase in the cost of a post-FIT colonoscopy. However, such benefit must be matched with the accelerated carcinogenesis simulated in the FIT-positive-colonoscopy setting, resulting in a higher-than-expected absolute benefit. FIT-positive patients are 5-fold enriched in advanced adenomas as compared with a primary colonoscopy population [24], leading to a 2,407 increase in the absolute numbers of CRC simulated when comparing FIT-positive and primary screening colonoscopy settings, respectively. Second, even in a public health system, the cost of treatment/palliation for CRC is still of a different magnitude as compared with the cost of a post-FIT-positive

▶ **Table 3** Effect, cost, and net benefit for a cohort of 100,000 subjects undergone standard colonoscopy or colonoscopy + GI GENIUS: "real-world practice" scenario results.

	Standard colonoscopy	Colonoscopy + GI GENIUS system
CRC cases	1,810	1,676
CRC prevented (95% CI)	–	134 (–135 to 370)*
% CRC prevented (95% CI)	–	7.4% (–7.7 to 28.2)*
CRC deaths	741	685
CRC deaths prevented (95% CI)	–	56 (–54 to 160)*
% CRC deaths prevented (95% CI)	–	–7.6% (–7.8 to 29.2)*
Life-years gained (95% CI)	–	1,309 years (–1,250 to 3,689)*
Gain in quality of life per person (95% CI)	–	0.010 QALY (–0.05 to 0.07)†
Total cost (per person)	€484.74	€479.83
Screening cost (per person)	€92.53	€102.52
Cost of care for adenoma (per person)	€146.50	€151.02
Cost of care for CRC (per person)	€245.71	€226.28
Total savings (per person) (95% CI)	–	€4.91 (–32.65 to 40.54)†
ICUR vs standard colonoscopy (incremental cost per QALY gained)	–	Dominant

CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; ICUR, incremental cost-utility ratio; QALY, quality-adjusted life-years.
*Colonoscopy + GI GENIUS system was more effective than standard colonoscopy in more than 85% of simulations.
†Colonoscopy + GI GENIUS system was more cost-effective than standard colonoscopy in more than 60% of simulations.

colonoscopy – €7,253 for CRC surgery or €13,760 for systemic chemotherapy vs €1,353.75 – so that the savings coming from the aversion of cancer treatment is exponential as compared with the linear increase in the cost of the preventive intervention.

The main assumption of our model is an inverse relationship between the increase in ADR due to AI intervention and the degree of CRC prevention. It could be argued that such a relationship has been clearly shown in the primary screening colonoscopy setting but not in FIT-positive populations. However, two different preliminary analyses of large FIT-positive databases confirmed such an ADR-CRC incidence inverse association, substantiating the result of our analysis [25, 26]. Second, our result is based on the assumption of an AI-driven ADR increase in the post-FIT-positive setting. Despite most of the ADR-benefit of CADe being shown in a non-FIT-positive setting, a recent study has shown the favorable effect also in the setting of FIT-positive

colonoscopy, which is exactly the scenario simulated in our model [18].

The cost-saving profile of our simulation should not marginalize the relevance of the initial investment. The financial resources required to purchase the AI machines are expected to occur simultaneously at the time of the intervention, while the savings require a longer perspective. Thus, a budget analysis based on the actual sustainability of a widespread AI implementation in the setting of public-funded organized screening programs is also necessary. However, after 5 years of simulation, the initial investment cost for AI was completely offset by the savings due to CRC cases prevented (**Fig. S2**). Moreover, among the Italian general population aged 50 to 65 years, participation in a CRC screening program is about 45% [27] and 4.1% resulted in FIT-positive [11], resulting in 261,076 potential colonoscopies performed leading to a total potential savings for the Italian NHS of about €3.7 million. The savings could increase up to almost €5.5 million for higher participation rates (65%) as observed in northern Italy.

The main weakness of our simulation is the uncertainty related to the natural history of CRC in a FIT-positive setting and the long-term efficacy of AI intervention. However, recent evidence confirms the increased CRC risk for a FIT-positive population not undergoing recommended colonoscopy [19] and our estimates are in line with the only model that simulated CRC carcinogenesis in a FIT-positive setting [18]. Similarly, the efficacy of CADe-assisted colonoscopy that we simulated in a separate subanalysis on primary screening colonoscopy is in line with recent modeling of the same population, which also demonstrated an overall cost savings utilizing AI-assisted screening colonoscopy [24].

Conclusions

In conclusion, we showed that the higher degree of CRC prevention that may be triggered by the additional increase in colorectal neoplasia by GI GENIUS-assisted colonoscopy results in a net savings of €14.34 euro per person, supporting the long-term sustainability of such an intervention in an organized CRC screening program.

Acknowledgement

Conflict of Interest

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