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COST-EFFECTIVENESS ANALYSIS OF ARTIFICIAL INTELLIGENCE-AIDED COLONOSCOPY FOR ADENOMA DETECTION AND CHARACTERISATION IN SPAIN

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Abstract:

Objective. To assess the cost-effectiveness of an Intelligent Endoscopy Module for computer-assisted detection and characterization (CADe/CADx) compared to standard practice, from a Spanish National Health System perspective.

Methods. A Markov model was designed to estimate total costs, life years gained (LYG), and quality-adjusted life years (QALYs) over a lifetime horizon with annual cycles. A hypothetical cohort of 1,000 patients eligible for colonoscopy (mean age of 61.32 years) was distributed between Markov states according to polyp size, location, and histology based on national screening programs' data. CADe/CADx efficacy was determined based on adenoma miss rates, and natural disease evolution was simulated according to annual transition probabilities. Detected polyps' management involved polypectomy and histopathology in standard practice, while with CADe/CADx leave-in-situ strategy was applied for ≤5mm rectosigmoid non-adenomas and resect-and-discard strategy for the rest of ≤5mm polyps. Unit costs (€,2024) included the diagnostic procedure and polyp and CRC management. A 3% annual discount rate was applied to costs and outcomes. The model's inputs were validated by an expert panel.

Results. CADe/CADx resulted more effective (16.37 LYG and 14.32 QALYs) than standard practice (16.33 LYG and 14.27 QALYs) over a lifetime horizon. Total cost per patient was €2,300.76 with CADe/CADx and €2,508.75 with colonoscopy alone. In a hypothetical cohort of 1,000 patients, CADe/CADx avoided 173 polypectomies, 370 histopathologies, and 7 CRC cases. Sensitivity analyses confirmed the model's robustness.

Conclusions. The results of this analysis suggest that CADe/CADx would result in a dominant strategy versus standard practice in patients undergoing colonoscopies in Spain.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1. Parameters employed in the one-way sensitivity analysis

- The discount rate for both costs and health outcomes was modified to 0% and 5%.
- The starting age of the initial cohort considered in the base case was modified to a median age of 50 years, representing the recommended age for participation in CRC screening programmes [8].
- The distribution of the initial cohort between the different health states was modified. Instead of the national proportions used on the base case, data from CRC screening programs of specific regions were used. To reflect extreme scenarios, data reported for the programmes of Galicia [26] and Castilla Leon [28] were chosen.
- The probability of a healthy person developing a ≤5 mm adenoma was varied by applying the standard deviation reported by Coretti et al. 2020 [31] to the mean value applied in the base case analysis for each age range (50-54 years, ±0.3%; 55-59 years, ±0.4%; 60-64 years, ±0.4%; 65-69 years, ±0.5%; ≥70 years, ±0.6%).
- The evolution of lesions to a larger size was modified by applying the standard deviation reported by Coretti et al. 2020 [31] to the value considered in the base case (from ≤5 mm to 6-9 mm, ±1.3%; from 6-9 mm to ≥10 mm, ±0.8%), and the evolution of a ≥10 mm adenoma to iCRC was modified according to the range provided by Frazier et al. 2000 [32] (2.0%-10.0%). Additionally, the evolution of a ≥10 mm adenoma to iCRC was modified with an alternative value (37.0%) coincident with the one considered in an Italian cost-effectiveness analysis of GI Genius compared to standard practice [42].
- The evolution of CRC varied based on the standard deviation reported by Coretti et al. 2020 [31] around the mean value applied on base case analysis (CRC I to CRC II, ±1.7%; CRC II to CRC III, ±8.4%; CRC III to CRC IV, ±1.2%).
- An equivalent management strategy, leave-in-situ, was applied for ≤5 mm RS No-A for both assessed alternatives, GI Genius, and standard practice involving only colonoscopy, as although this strategy is not recommended in clinical guidelines, clinical experts consulted mentioned that such a strategy is currently used in some hospitals.

- The unitary cost of colonoscopy varied according to the lowest and highest tariffs identified (Aragón: € 77.56; and Navarra: € 700.35) [36].
- The cost of GI Genius per colonoscopy was modified by applying a 15% reduction to the cost used in the base case.
- The unitary costs for polypectomies and histopathology analyses used in the base case analysis for the estimation of the cost of lesion management were modified within the range of ±10%.
- The annual costs of CRC management varied within ±10%.
- Utilities for polyp and no polyp health states were modified with alternative values reported in the literature [44]. Utilities for the different CRC stages varied based on the standard deviation reported in Coretti et al. 2020 [31].
- The LMR of both GI Genius and standard clinical practice was modified to the values considered in the Italian cost-effectiveness model of GI Genius compared to standard practice [42]. A GI Genius LMR of 17.26%, 8.28%, and 7.60% was considered for ≤5 mm, 6-9 mm, and ≥10 mm lesions, respectively. For standard practice, the LMR was 31.00% for ≤5 mm, 19.00% for 6-9 mm, and 9.00% for ≥10 mm lesions.

Supplementary Material 2. Distributions and parameters employed in the probabilistic sensitivity analysis

Parameters		Deterministic value	Distributions	Alpha	Beta
Lesion miss rate					
GI Genius	≤ 5 mm RS No-A	15.85%	Beta	16	84
	≤ 5 mm RS A	15.85%	Beta	16	84
	≤ 5 mm No-RS No-A	15.85%	Beta	16	84
	≤ 5 mm No-RS A	15.85%	Beta	16	84
	6-9 mm	20.69%	Beta	21	79
	≥ 10 mm	6.06%	Beta	6	94
Standard practice	≤ 5 mm RS No-A	35.75%	Beta	36	64
	≤ 5 mm RS A	35.75%	Beta	36	64
	≤ 5 mm No-RS No-A	35.75%	Beta	36	64
	≤ 5 mm No-RS A	35.75%	Beta	36	64
	6-9 mm	22.86%	Beta	23	77
	≥ 10 mm	15.79%	Beta	16	84
Transition from healthy patient to patient with ≤ 5 mm adenoma					
50-54 years old		0.80%	Beta	1	99
55-59 years old		1.00%	Beta	1	99
60-64 years old		1.20%	Beta	1	99
65-69 years old		1.30%	Beta	1	99
≥ 70 years old		1.50%	Beta	2	98
Evolution of lesions					
From ≤ 5 mm to 6-9 mm		3.50%	Beta	4	96
From 6-9 mm to ≥ 10 mm		2.20%	Beta	2	98
≥ 10 mm to iCRC		5.00%	Beta	5	95
Distribution at follow-up colonoscopy					
≤ 5 mm RS No-A		53.78%	Dirichlet	53.78	11.30
≤ 5 mm RS A		8.19%		8.19	7.20
≤ 5 mm No-RS No-A		9.66%		9.66	18.04
≤ 5 mm No-RS A		28.36%		28.36	75.28
Evolution of CRC					
CRC stage I to CRC stage II		23.80%	Beta	24	76
CRC stage II to CRC stage III		48.50%	Beta	49	51
CRC stage III to CRC stage IV		30.20%	Beta	30	70

Parameters		Deterministic value	Distributions	Alpha	Beta
Annual recurrence risk					
CRC stage I		5.80%	Beta	6	94
CRC stage II		5.80%	Beta	6	94
CRC stage III		18.80%	Beta	19	81
CRC stage IV		18.80%	Beta	19	81
Utilities					
No polyp health state		0.88	Beta	88	12
Polyp health state		0.88	Beta	88	12
CRC stage I health state		0.74	Beta	74	26
CRC stage II health state		0.74	Beta	74	26
CRC stage III health state		0.59	Beta	59	41
CRC stage IV health state		0.25	Beta	25	75
Costs					
GI Genius		€ 7.59	Gamma	44	0.17
Colonoscopy		€ 326.98	Gamma	44	7.36
Polypectomy		€ 133.55	Gamma	44	3.00
Histopathology		€ 152.23	Gamma	44	3.43
CRC management	CRC stage I	€ 4,211.61	Gamma	44	94.76
	CRC stage II	€ 4,700.04	Gamma	44	105.75
	CRC stage III	€ 4,714.16	Gamma	44	106.07
	CRC stage IV	€ 7,833.94	Gamma	44	176.26

A: Adenoma; CRC: Colorectal cancer; iCRC: Interval colorectal cancer; RS: Rectosigmoid

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant neoplasm, accounting for approximately 10% of all cancer cases, and the second leading cause of cancer-related deaths worldwide [1]. In Spain, CRC is the most commonly diagnosed tumour, with an estimated 42,721 new cases in 2023 [2]. Population-based CRC screening programs have been implemented to resect precursor lesions and diagnose CRC in earlier stages, decreasing the incidence and mortality of CRC and leading to a better prognosis [3]. In Spain, these programs are carried out in individuals aged 50-69 years through a biennial faecal immunochemical test (FIT), which, if positive, is followed by a colonoscopy [4].

The efficacy of population-based CRC screening programs depends on the detection rate of precursor lesions during colonoscopy [5], which is far from perfect. A recent meta-analysis reported adenoma miss rates (AMR) of 26%, 9%, and 27% for adenomas, advanced adenomas, and serrated polyps, respectively [6]. Similarly, lesions missed during colonoscopy account for 50%-60% of interval CRC (iCRC) cases [6].

On the other hand, an increased detection rate results in a higher number of polypectomies and histopathology analyses. However, more than 90% of polyps found in screening colonoscopy are less than 10 mm in size, and 85% are less than 6 mm [7]. In addition, the prevalence of advanced histology in diminutive polyps is less than 0.5% [8]. Within this context, the introduction of resect-and-discard and leave-in-situ strategies has been proposed to decrease the risks and costs of polypectomy and histopathology analyses of diminutive polyps [9][12]. Nevertheless, these strategies have not been implemented in clinical practice mainly because of the great variability in efficacy, diagnostic accuracy, and failure to meet standards [10].

In recent years, artificial intelligence (AI)-based systems have been developed that may help to overcome these issues. The integration of AI systems can enhance the efficiency and accuracy of adenoma detection and characterisation through real-time pattern recognition [11]. Indeed, it has been consistently shown that the use of computer-assisted detection (CADe) systems can increase the adenoma detection rate [11,12]. Additionally, several studies have described the good performance of

computer-assisted characterisation (CADx) in terms of differentiating diminutive polyps, with a negative predictive value (NPV) for diagnosing adenoma exceeding 90% [13]. To date, only one study has evaluated the performance of an AI system to fulfil the criteria to apply the resect-and-discard and leave-in-situ strategies, which has shown that the GI Genius CADe/CADx technology meets the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) requirements for the implementation of these strategies [9,14].

The implementation of a CADe system is likely to increase healthcare costs in the short term as more lesions are detected, but this could be balanced in the long term by CRC management savings [15]. Additionally, the implementation of a CADx system could further reduce costs by reducing polypectomies and histopathological assessments [14]. However, there is little evidence of the cost-effectiveness in this context. Thus, it is important to explore the economic benefits of implementing CADe and CADx solutions to determine the feasibility of adopting such technology in healthcare settings with limited resources.

Therefore, the present analysis aimed to assess the cost-effectiveness of GI Genius CADe/CADx technology compared to standard clinical practice in patients eligible for colonoscopy in Spain.

METHODS

A Markov model was conceptualized and designed to represent the clinical pathway of patients undergoing colonoscopy for primary CRC screening, for polypectomy surveillance, to follow up on a positive FIT result, or because they present any suspicious symptoms or signs. Eight mutually exclusive main Markov states were established: colonoscopy, no polyp, polyp, CRC I, CRC II, CRC III, CRC IV, and death (Figure 1). In addition, within the polyp state, different substates were considered to incorporate the characterisation of these polyps, and they were classified according to their size (≤5 mm, 6-9 mm, or ≥10 mm). Furthermore, polyps ≤5 mm were also classified according to their location [rectosigmoid (RS), or no rectosigmoid (No- RS)] and histopathology [adenoma (A) or no adenoma (No-A)].

A cost-effectiveness model was developed in Microsoft Excel 365 MSO (version 2409) to estimate, over a lifetime horizon with annual Markov duration cycles, the total cumulative costs, and total health

outcomes, in terms of life years gained (LYG) and quality-adjusted life years (QALYs). The population considered in the analysis consisted of a hypothetical cohort of 1,000 adult patients eligible for colonoscopy, with a mean age of 61.32 years at model entry.

At the beginning of the simulation, the assessed cohort of patients, who presented an initial distribution of different clinical situations based on the available evidence (absence of polyps, presence of polyps of different sizes, locations, and histology, or CRC stage), underwent an index colonoscopy (i.e., the first colonoscopy or a follow-up colonoscopy). The detection rates differed between patients who underwent colonoscopy with standard practice and patients who underwent colonoscopy with GI Genius. Those patients with undetected lesions could progress to larger lesions or even to iCRC in the period until the next follow-up colonoscopy. Patients in whom a lesion was detected received the appropriate management strategy according to their diagnosis and were then considered to constitute a healthy population. However, during the follow-up period, the healthy population could develop new ≤5 mm lesions, which could also evolve into larger lesions and could even progress to cancer. At the time of the next follow-up colonoscopy in both groups of patients, the detection rate corresponding to each type of lesion was reapplied, and the corresponding management and follow-up strategies were repeated for each case.

Patients diagnosed with CRC were classified according to the CRC stage (CRC stage I, CRC stage II, CRC stage III, and CRC stage IV) and could progress from early to advanced stages. At any time during the simulation, there was a risk of death either due to general causes or due to the clinical situation of the patient.

This study was conducted from the perspective of the National Health System (NHS) of Spain to illustrate the efficiency of incorporating AI-assisted colonoscopy for the detection and characterisation of polyps and CRC. An annual discount rate was applied to both costs and health outcomes, in line with national guidelines' recommendations for the development of a cost-effectiveness analysis [16]. The model considered a 3.00% annual discount rate according to the published recommendations for Spain [16].

Panel of experts

The model structure and all the input values necessary for the development of the analysis were validated and agreed upon by a panel of 3 endoscopists with extensive expertise, experience, and knowledge of the disease and the CRC screening program. To this end, a structured questionnaire was developed with all the parameters identified in the scientific literature that were proposed for use in the model. This questionnaire was individually completed by the experts, and subsequently, two face-to-face consensus meetings were held to validate and agree on values and assumptions when needed.

Interventions assessed

The analysis compared two different interventions for the early detection of malignancies: GI Genius Intelligent Endoscopy Module-assisted colonoscopy versus the current standard clinical practice (i.e., colonoscopy alone).

Clinical data

At the beginning of the simulation, based on data reported in national screening programmes and available evidence identified in the scientific literature [14,17–21], the population was stratified based on different health states and substates, the absence of polyps (33.15%), the presence of lesions of different sizes, locations and histology [≤5 mm RS No-A (14.80%), ≤5 mm RS A (2.25%), ≤5 mm No-RS No-A (2.66%), ≤5 mm No-RS A (7.80%), 6-9 mm (21.61%), ≥10 mm (13.91%)], and the presence of CRC [CRC stage I (0.84%), CRC stage II (1.03%), CRC stage III (1.09%) and CRC stage IV (0.86%)].

The efficacy of GI Genius was determined for each lesion size based on the lesion miss rate (LMR) described as AMR in a prospective randomized study carried out in 8 centres in Italy, the United Kingdom, and the United States (Table 1) [12]. The population with undetected lesions was calculated using the LMR, whereas the number of patients with detected lesions was calculated using the complementary value of the LMR.

The management of the lesions was performed based on a consensus document on the follow-up of patients after lesion resection during colonoscopy [22]. Polypectomy and histopathology for any lesion were considered standard practices regardless of its size, histology, or location. When GI Genius was used, based on the PIVI criteria endorsed by American guidelines, the leave in-situ strategy was applied for ≤5 mm RS No-A lesions, and the resect and discard strategy was applied for the other lesions ≤5 mm (≤5 mm RS A, ≤5 mm No-RS No-A and ≤5 mm No-RS A) (Table 1) [9]. Finally, the management of lesions >5 mm involved both polypectomy and histopathology. Regarding post-colonoscopy follow-up surveillance, a 10-year interval was considered for patients without lesions and patients with lesions <10 mm, and a 3-year interval was considered for patients with lesions ≥10 mm (Table 1) [22].

The natural evolution of the disease was simulated according to the annual transition probabilities between the different health states identified in the literature [23–25]. All lesions except ≤5 mm RS No-A lesions could grow in size [23] or progress to iCRC [24]. Moreover, within the CRC state, patients could also experience recurrences associated with worsened outcomes (Table 1) [25].

Mortality

All-cause mortality data were considered in the model to reflect the annual probability of death and stratified by age and sex. Standardized rates for the Spanish population were obtained from the National Statistics Institute [26]. Given that CRC patients have a higher risk of death than the general population, the analysis considered specific CRC-related mortality from available literature data (Table 1) [25].

Utilities

To estimate the cumulative QALYs, different utility values reported in the scientific literature [23,27] for each of the health states were considered to assess the impact on patients' quality of life. Health state-specific utility values were derived from EuroQol 5 Dimension (EQ-5D) questionnaire scores [27]. All the utilities are described in detail in Table 2.

Resource consumption and costs

In line with the perspective adopted, only direct healthcare costs were considered in the analysis, including diagnostic procedures and disease management costs per health state. All costs are expressed in euros, 2024-year value (€, 2024).

Regarding diagnostic procedure cost, colonoscopy and the acquisition of the GI Genius were considered. The cost of colonoscopy (€ 326.98) was derived by averaging the unitary tariffs identified through a national database that collects health costs from different sources [28] (Table 2). The cost of GI Genius for each colonoscopy (€ 7.59) was estimated by considering an average cost of € 45,000 per intelligent endoscopy module, which included 3 years of software updates and support and allowed for 1,976 colonoscopies per year (assuming the use in a room that is active 8 hours per day with an average duration per colonoscopy of 1 hour over the 247 working days estimated per year) (Table 2).

The cost of disease management was established by the health state. For the estimation of the cost of lesion management, polypectomies, and histopathology analyses were considered, as well as the facultative visits per colonoscopy associated with the communication of histopathology findings. The polypectomies and facultative visit unitary costs were estimated as the average of the unitary tariffs identified [28], and the cost of histopathology was obtained from the literature [29] (Table 2). The annual costs associated with CRC management at each stage of the disease were derived from a retrospective observational study carried out in Spain [17] (Table 2). These costs were updated to 2024 values with the general consumer price index reported by the Spanish National Statistics Institute [26].

Cost-effectiveness analysis

For each of the interventions assessed in the model, total costs and QALYs gained were estimated. The efficiency was expressed as an incremental cost-utility ratio (ICUR) in terms of cost per additional QALY with GI Genius-assisted colonoscopy versus colonoscopy performed without AI according to the current standard of clinical practice.

Although in Spain, there is no officially established threshold of willingness to pay, a strategy is usually considered cost-effective when the ICUR versus the alternative option is below a cost-utility threshold

of € 25,000/QALY gained [30]. Moreover, when a strategy is as or more effective and less costly than the alternative option, it is considered to be a dominant strategy [31].

Sensitivity analyses

Sensitivity analyses (SA), including one-way SA (OWSA) and probabilistic SA (PSA), were performed to assess the robustness of the model and the uncertainty around the parameter values considered in the analysis.

To carry out OWSA, the following parameters were varied individually: discount rate, mean age of the initial cohort, initial distribution of patients, LMR, probability of a healthy person developing a ≤5 mm adenoma, lesions, and CRC evolution, management strategy of ≤5 mm RS No-A lesions, utility values, colonoscopy cost, GI Genius cost, lesion management cost and CRC management cost (Supplementary Material 1).

The PSA was performed through 10,000 Monte Carlo iterations to assess the impact of model parameters by simultaneously varying their values. A beta distribution was chosen to modify the LMR, the probability of healthy patients developing a ≤5 mm adenoma, the evolution of lesions and CRC, the risk of CRC recurrence, and utilities. The distribution of patients at follow-up colonoscopy was modified with a Dirichlet distribution, and a gamma distribution was used for unitary resource costs (colonoscopy, GI Genius per colonoscopy, polypectomies, and histopathology) and annual CRC management costs (Supplementary Material 2).

RESULTS

Base case

During the simulation, for a cohort of 1,000 persons eligible for undergoing a colonoscopy, GI Genius was associated with the performance of 2,879 colonoscopies, 574 polypectomies, 377 histopathology analyses, and the detection of 44 CRC cases. In comparison, standard clinical practice was associated with 2,863 colonoscopies, 747 polypectomies, 747 histopathology analyses, and the detection of 51 CRC cases. Therefore, the use of GI Genius at colonoscopy avoided 173 polypectomies, 370 histopathology analyses, and 7 cases of CRC due to early-stage detection of lesions.

Over a lifetime horizon, GI Genius was associated with 16.37 LYG and 14.32 QALYs and resulted in a more effective option compared to current standard practice (16.33 LYG and 14.27 QALYs).

The total cost per patient at the end of the simulation was € 2,300.76 with GI Genius-assisted colonoscopy and € 2,508.75 with colonoscopy alone.

Based on these results, GI Genius was considered a dominant option, i.e., it is more effective and less costly than standard clinical practice in a population undergoing colonoscopies for CRC detection in Spain (Table 3).

Sensitivity analyses

The results of SA confirmed the robustness of the model´s base case results in the simulations. GI Genius was a dominant strategy compared to standard clinical practice for all OWSAs performed. The parameter that most influenced the results was the LMR, followed by the discount rate. Variations in the LMR resulted in variations in the ICUR ranging from -4,513/QALY gained to € -7,789/QALY gained, indicating that this parameter influences the results of the analysis. A decrease in the discount rate (0%) caused an increase in the ICUR up to € -3,597/QALY gained. On the other hand, an increase in the discount rate (5%) caused a reduction in the ICUR up to € -5,267/QALY gained (Figure 2).

The PSA results showed that GI Genius was a dominant strategy in 92.91% of the 10,000 simulations performed, with lower costs (average savings of € 204.22) and greater effectiveness (average gain of 0.04 LYG and 0.04 QALYs). The results of each of the simulations are shown in the cost-effectiveness plane (Figure 3).

DISCUSSION

This analysis shows that although the implementation of AI-aided colonoscopy requires an initial investment, the use of GI Genius over a lifetime horizon results in increased effectiveness and a reduction in the costs for the NHS. The increase in effectiveness is explained by increased survival, with better quality of life (16.37 LYG and 14.32 QALYs with GI Genius compared to 16.33 LYG and 14.27 QALYs with current standard practice per patient). The feasible rationale is that a reduced LMR results in a better diagnostic yield and treatment of precursor lesions before they become cancerous. The reduction of € 207.99 per patient can be explained by a reduction in CRC management costs due to earlier detection of CRC cases and a reduction in CRC cases because of increased detection of lesions before they can progress to carcinoma. Additionally, these differences in total costs can also be justified by the avoidance of polypectomies and histopathology analyses; while more lesions are detected with the use of AI, the introduction of the CADx module enables cost-saving strategies to be implemented (leave-in-situ and resect-and-discard), resulting in a reduction in the number of polypectomies and histopathology analyses performed [14]. Therefore, the economic benefits of AI may also extend beyond lesion detection to lesion characterisation.

In the current context of the NHS in Spain, where resources available for health care are limited, cost-saving strategies based on an optical diagnosis of colorectal lesions are required to reduce the economic burden of polypectomy and histological diagnosis, as well as the risks associated with endoscopic resection. Nevertheless, the implementation of the leave-in-situ strategy for ≤5 mm RS hyperplastic lesions and the resect-and-discard strategy for more proximal ≤5 mm lesions has been hindered partly by the suboptimal accuracy reported by the endoscopy community [10] and because the minimum cut-off values required to incorporate this paradigm in clinical practice have not been reached [9]. AI programs thus have the potential to improve the overall prediction of histology based on endoscopic imaging, thereby democratizing access to enhanced diagnostic results. Consequently, this may lead to improved health equity and increased NHS efficiencies while also yielding potential cost savings [14]. So far, as a previous cost-effectiveness analysis focused on the detection of lesions, the reduction in costs derived from the use of AI during colonoscopies was only centred on the

avoidance of CRC, implying long-term savings. However, in our analysis, after considering AI-guided characterisation of lesions and thus applying leave-in-situ and resect-and-discard strategies, a cost reduction per patient was observed from the first year of the simulation, when colonoscopies were performed, due to the management of detected lesions and the reduction of polypectomies and histopathological analyses. Furthermore, in the era of climate change and global warming, the opportunity to greatly reduce greenhouse gas emissions related to gastrointestinal pathology processing would be an additional benefit associated with the use of AI [32].

To the authors' knowledge, this is the first cost-effectiveness analysis exploring the benefits of adding both the detection and characterisation modules to AI-assisted colonoscopies, as previously published economic evaluations studying the addition of AI to colonoscopies only included the consequences of using the CADe module. Additionally, this study is the first economic evaluation in the Spanish context comparing the use of GI-Genius with current standard practices in patients undergoing colonoscopy. Previously published analyses have evaluated the efficiency of GI-Genius detection in other countries, such as Italy and Canada [33,34]. The findings of this study are in line with other cost-effectiveness analyses previously published in the literature, indicating that the incorporation of the detection module of GI-Genius results in a more effective and less costly alternative than the use of standard clinical practice [33,34]. Interventions that are more effective and less expensive than their comparator, known as dominant alternatives, should always be accepted in decision-making, as their adoption generates better clinical outcomes while saving system resources [31].

There are some limitations in the present model that should be considered when interpreting the results. First, there are potential limitations inherent to the nature of this type of economic evaluation. For instance, the theoretical nature of cost-effectiveness analyses may not be an exact representation of clinical practice. In this sense, the influence of the number of lesions presented per patient was not considered in the analysis, as it added more complexity to the model and thus uncertainty. Nevertheless, available guidelines on CRC screening and lesion management were followed to design the structure of the model [4,22]. Similarly, the model considered GI-Genius to be 100% accurate for

polyp characterisation to avoid introducing more complexity to the simulation. The accuracy of GI-Genius in real life will certainly be lower, but data are scarce. An Italian study showed an overall accuracy of 86.8% for lesions ≤ 5 mm, with a slight increase in the rectosigmoid (91.8%) and an NPV of 97.6% for the rectosigmoid lesion [14]. More reliable data are needed before introducing this variable into an economic analysis. Additionally, adverse events related to polypectomies were not considered because of their low incidence, the difficulty involved in quantifying this incidence due to the large variation in the literature, and the complexity it would have added to the model. Nonetheless, if considered, the costs associated to adverse events after polypectomies should have been less with GI Genius, as fewer polypectomies are performed.

Additionally, due to a lack of available data, assumptions related to the natural evolution of the pathology need to be made. The LMR and the evolution of lesions depend only on their size and not on their location or histopathology. Moreover, it was assumed that all 6-9 mm and ≥10 mm lesions were adenomas, as, according to the experts' opinion, the percentage of no adenomatous lesions of these sizes was very low. For lesion detection, it was assumed that there were no false positives. Moreover, it was assumed that there was no risk of discarding invasive cancer, as the prevalence of invasive cancer in diminutive polyps is very low [35] and considering it would have included more complexity to the model. Finally, when no data were available for the Spanish context in the literature, values from other countries were selected. However, all parameters and assumptions included in the analysis were validated by a panel of clinical experts with experience and expertise in CRC screening.

Despite the above limitations and the assumptions considered in the analysis, the results of the SA confirm the robustness of the model, as the uncertainty associated with the parameters used in the modelling did not show a significant deviation from the results obtained in the base case, with the use of GI Genius being a dominant strategy in all simulations.

In conclusion, the results of the present model suggest that the use of the GI Genius CADe and CADx modules could be considered a dominant strategy (i.e., it is more effective and less costly) compared to standard clinical practice in patients undergoing colonoscopies in Spain. Moreover, this analysis

confirmed that the use of a computer-aided colonoscopy with GI Genius for CRC screening can help to avoid polypectomies and histopathology analyses and improve the detection of CRC precursor lesions.

FIGURE LEGENDS:

- Figure 1. Markov model diagram
- Figure 2. Deterministic sensitivity analysis. Tornado diagram
- Figure 3. Probabilistic sensitivity analysis. Cost-effectiveness plane

Table 1. Clinical data

Lesion miss rate		GI Genius		Standard practice	Reference
≤5 mm RS No-A		15.85%		35.75%	[12]
≤5 mm RS A		15.85%		35.75%	[12]
≤5 mm No-RS No-A		15.85%		35.75%	[12]
≤5 mm No-RS A		15.85%		35.75%	[12]
6-9 mm		20.69%		22.86%	[12]
≥10 mm		6.06%		15.79%	[12]
Detected lesions' management		GI Genius		Standard practice	
≤5 mm RS No-A		Leave-in-situ		Polypectomy + histopathology	[9,22]
≤5 mm RS A		Resect and discard		Polypectomy + histopathology	[9,22]
≤5 mm No-RS No-A		Resect and discard		Polypectomy + histopathology	[9,22]
≤5 mm No-RS A		Resect and discard		Polypectomy + histopathology	[9,22]
6-9 mm		Polypectomy + histopathology		Polypectomy + histopathology	[9,22]
≥10 mm		Polypectomy + histopathology		Polypectomy + histopathology	[9,22]
Transition from healthy patient to patient with ≤5 mm adenoma					
50-54 years old		0.80%			[23]
55-59 years old		1.00%			[23]
60-64 years old		1.20%			[23]
65-69 years old		1.30%			[23]
≥ 70 years old		1.50%			[23]
Evolution of lesions					
From ≤5 mm to 6-9 mm		3.50%			[23]
From 6-9 mm to ≥10 mm		2.20%			[23]
≥10 mm to iCRC		5.00%			[24]
Evolution of CRC					
CRC stage I to CRC stage II		23.80%			[23]
CRC stage II to CRC stage III		48.50%			[23]
CRC stage III to CRC stage IV		30.20%			[23]
Annual recurrence risk					
CRC stage I		5.80%			[25]
CRC stage II		5.80%			[25]
CRC stage III		18.80%			[25]
CRC stage IV		18.80%			[25]
Distribution at follow-up colonoscopy					
≤5 mm RS No-A		53.78%			[14]
≤5 mm RS A		8.19%			[14]
≤5 mm No-RS No-A		9.66%			[14]
≤5 mm No-RS A		28.36%			[14]
CRC annual mortality rate		<65 years	65–75 years	>75 years	
CRC stage I	No recurrent	3.00%	5.00%	10.50%	[25]
	Recurrent	56.00%	56.00%	87.00%	[25]
CRC stage II	No recurrent	3.00%	5.00%	10.50%	[25]
	Recurrent	56.00%	56.00%	87.00%	[25]
CRC stage III	No recurrent	5.00%	8.50%	16.50%	[25]
	Recurrent	68.00%	67.00%	93.50%	[25]
CRC stage IV	No recurrent	5.00%	8.50%	16.50%	[25]
	Recurrent	68.00%	67.00%	93.50%	[25]

A: Adenoma; CRC: Colorectal cancer; iCRC: Interval colorectal cancer; RS: Rectosigmoid

Table 2. Utilities and costs

Utilities			References
No polyp		0.88	[27]
Polyp		0.88	[27]
CRC stage I		0.74	[23]
CRC stage II		0.74	[23]
CRC stage III		0.59	[23]
CRC stage IV		0.25	[23]
Costs			
Colonoscopy		€ 326.98/per colonoscopy	[28]
GI Genius		€ 7.59/per colonoscopy	*Assumption*
Polypectomy		€ 133.55/per lesion	[28]
Histopathology*		€ 152.23/per lesion	[28,29]
CRC management	Stage I	€ 4,211.61/per annum	[17]
	Stage II	€ 4,700.04/per annum	[17]
	Stage III	€ 4,714.16/per annum	[17]
	Stage IV	€ 7,833.94/per annum	[17]

*This cost includes the cost of histopathology (€ 64.08) and the cost associated with a facultative visit (€ 88.15)
CRC: Colorectal cancer

Table 3. Base case results

	GI Genius	**Standard practice**	**Incremental** (GI Genius vs. standard practice)
Total LYG	16.37	16.33	0.04
Total QALYs	14.32	14.27	0.05
Total costs	€ 2,300.76	€ 2,508.75	€ -207.99
Diagnostic cost	€ 724.59	€ 704.09	€ 20.50
Disease management cost	€ 1,576.17	€ 1,804.66	€ -228.49
ICER (cost/LYG gained)	GI Genius resulted in a dominant option (more effective and less costly than current standard practice)		
ICUR (cost/QALY gained)	GI Genius resulted in a dominant option (more effective and less costly than current standard practice)		

ICER: Incremental cost-effectiveness ratio; ICUR: Incremental cost-utility ratio; LYG: Life years gained; QALYs: Quality-adjusted life years

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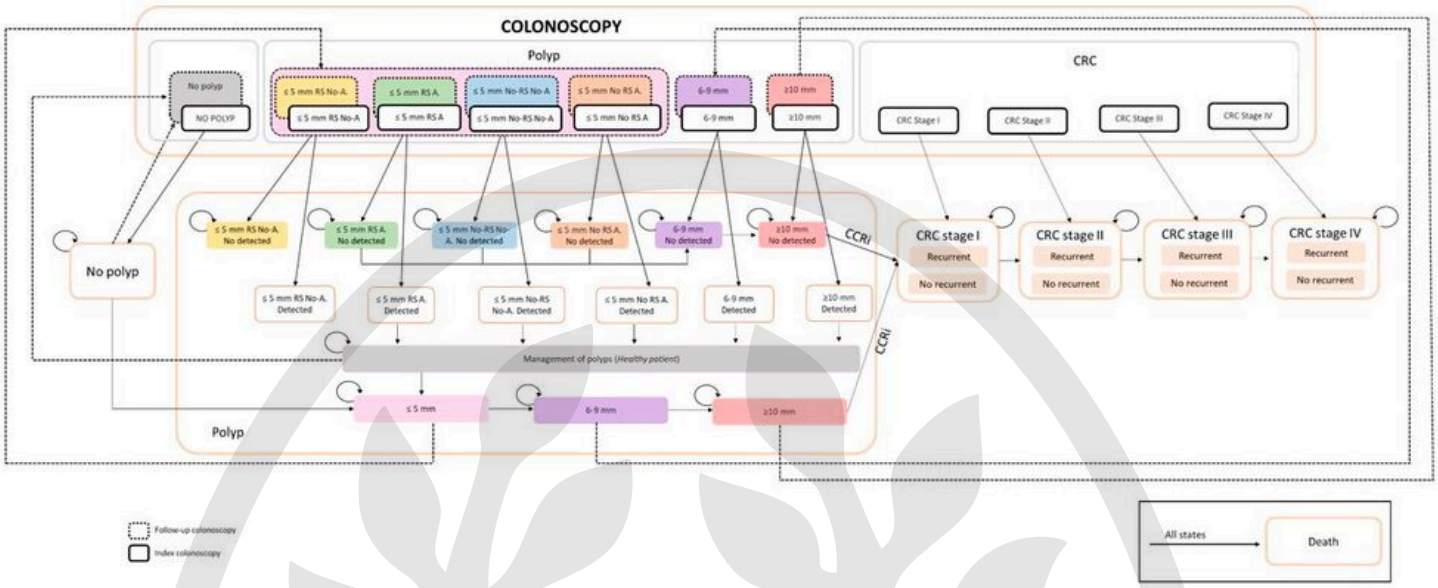
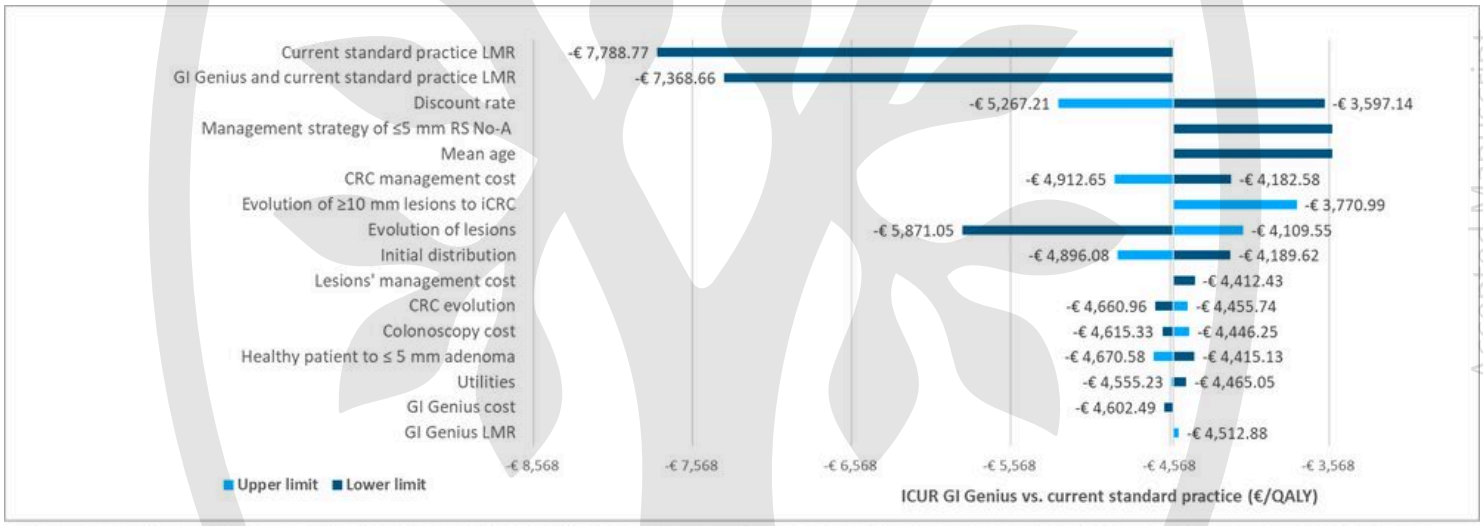
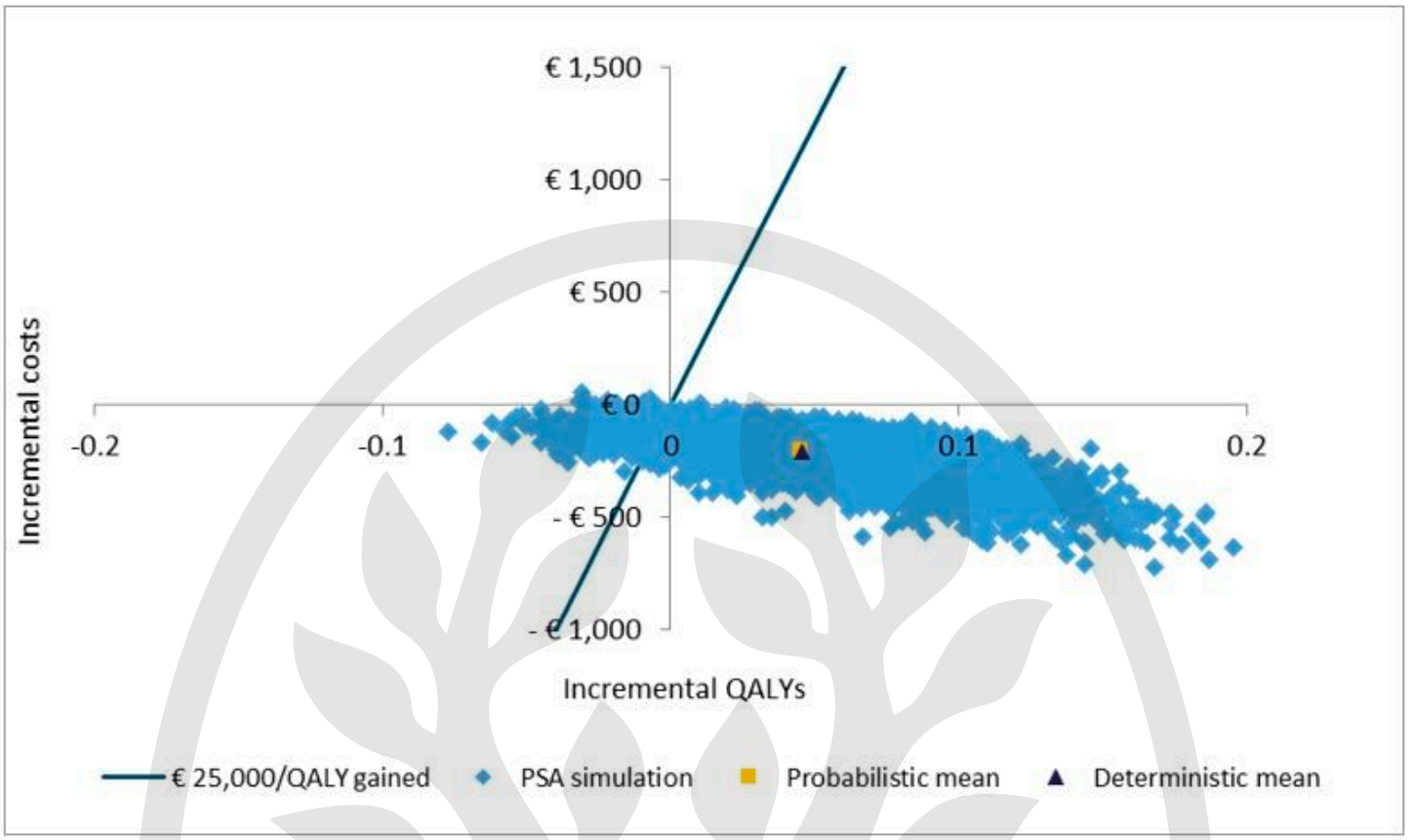


A: Adenoma; CRC: Colorectal cancer; iCRC: Interval colorectal cancer; RS: Rectosigmoid



A: Adenoma; CRC: Colorectal cancer; iCRC: Interval colorectal cancer: ICUR: Incremental cost-utility ratio; LMR: Lesion miss rate; RS: Rectosigmoid; QALY: Quality-adjusted life years



PSA: Probabilistic sensitivity analysis; QALYs: Quality-adjusted life years