Research Article

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# Cost-Effectiveness of Colorectal Cancer Screening in High-Risk Spanish Patients: Use of a Validated Model to Inform Public Policy

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## Abstract

**Background:** The European Community has made a commitment to colorectal cancer (CRC) screening, but regional considerations may affect the design of national screening programs. We developed a decision analytic model tailored to a pilot screening program for high-risk persons in Spain with the aim of informing public policy decisions.

**Materials and Methods:** We constructed a decision analytic Markov model based on our validated model of CRC screening that reflected CRC epidemiology and costs in persons with first-degree relatives with CRC in Aragón, Spain, and superimposed colonoscopy every 5 or 10 years from ages 40 to 80 years. The pilot program's preliminary clinical results and our modeling results were presented to regional health authorities.

**Results:** In the model, without screening, 88 CRC cases occurred per 1,000 persons from age 40 to 85 years. In the base case, screening reduced this by 72% to 77% and gained 0.12 discounted life years per person. Screening every 10 years was cost saving, and screening every 5 years versus every 10 years cost 7,250 euros per life year gained. Based on these savings, 36 to 39 euros per person per year could go toward operating costs while maintaining a neutral budget. If screening costs doubled, screening remained highly cost-effective but no longer cost saving. These results contributed to the health authorities' decision to expand the pilot program to the entire region in 2009.

**Conclusions:** Colonoscopic screening of first-degree relatives of persons with CRC may be cost saving in public systems like that of Spain. Decision analytic modeling tailored to regional considerations can inform public policy decisions.

**Impact:** Tailored decision analytic modeling can inform regional policy decisions on cancer screening.
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## Introduction

Colorectal cancer (CRC) is one of the most common malignancies in western countries. In Spain, it is the third most common cancer in men, behind prostate and lung cancer, and the second most common cancer in women, behind breast cancer (1). It has been estimated that, in 2010, 25,173 new CRC cases will be diagnosed in Spain (2). The mortality due to this cancer in Spain is ~50%, with similar figures reported in many other European countries (3-5).

CRC is potentially preventable by screening with strategies including fecal occult blood testing (FOBT), sigmoidoscopy, and colonoscopy among others. Screening is currently recommended in several European clinical guidelines (6). The recommended strategies vary according to CRC risk. Families with hereditary syndromes with very high risk of CRC should follow intense and specific screening and surveillance programs. First-degree relatives of patients diagnosed with CRC at a relatively young age are at increased risk, and screening colonoscopy is recommended for them starting at age 40 or 10 years before the diagnosis of CRC in the youngest affected relative (6, 7).

Real-world implementation of these guidelines may be hampered by constrained economic resources and the lack of implementation programs, especially within national health systems with universal access to health care. In Spain, no national CRC screening programs have been implemented, and only small initiatives have been undertaken in individual communities. The absence of appropriate studies establishing the cost-effectiveness of screening that take into consideration local or national population and health system characteristics has been a

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key element in delaying initiation of CRC screening programs across the country (6).

Aragón, with a population of ~1,300,000 people, is one of Spain's 15 autonomous regions. In 2002, Aragón's local government implemented a pilot program focused on persons at high risk of CRC, including first-degree relatives of patients with CRC. This commitment was based on cumulative evidence from published literature, the advice of expert health professionals, and the burden of CRC in the population (6, 8).

The cost-effectiveness of CRC screening has been addressed by multiple previous studies. However, the results of previous analyses might not be applicable to higher-risk patients in countries with widely accessible public health systems, like Spain. The aims of this study were to perform a decision analysis focusing on the real world scenario of Aragón and thereby inform local decision-making. We developed a tailored decision analytic model based on our published, validated CRC screening model. Our results contributed to the recent decision by health authorities to expand the pilot program to the entire region.

## Materials and Methods

### General study design

A previously published and validated model of CRC screening in average risk persons in the United States (9, 10) served as a feasibility model and formed the basis for our tailored model. A new model was first developed to reflect the epidemiology of CRC in the general population of Aragón, Spain. CRC incidence was then adjusted to reflect the higher risk experienced by persons with a first-degree relative with CRC. Local costs were used. Annual total budget impact for Aragón was estimated based on census data and mean total annual health care expenditures in Spain. The results were presented to regional health authorities responsible for setting health care policy and making budget decisions.

### Literature review and data sources

The sources for the original U.S. model inputs have been described previously (9-12). Epidemiologic data used to develop the model for Aragón were obtained from the Cancer Registry, General Directorate for Public Health, Government of Aragón; Mortality Registry, National Institute of Statistics, Spain; and the National Institute of Health, Spain.

### Decision analytic model

The original U.S. model and its calibration and validation have been described in detail (9-12). The model is constructed in TreeAge (TreeAge Software, Inc.). The original natural history model reproduces the natural history and age-specific incidence and prevalence of colorectal adenomas in autopsy series and of CRC in the United States without screening (9-12). Screening strategies are superimposed on the natural history model. The model's predictions for conventional strategies are consistent with available clinical data (9-15). As validation, we have modeled a cohort representing the one studied by Mandel et al. (13, 14) with FOBT offered and followed up as in that study, with excellent agreement between the model's predictions and the results of the clinical trial (10).

For the current analysis, we developed a model to reflect the epidemiology of CRC in Aragón and to estimate CRC incidence in persons at elevated risk of CRC conferred by a family history of CRC in a first-degree relative. Model inputs are shown in Table 1.

***Natural history.*** The principal health states in the model are (Fig. 1) normal; small (<10 mm) adenomatous polyp; large (≥10 mm) adenomatous polyp; localized, regional, or distant CRC; and dead. In the model, ~85% of CRCs develop through a potentially identifiable polypoid adenoma. In the Natural history model, CRCs are diagnosed with colonoscopy once they lead to symptoms. Diagnosed CRCs are treated, resulting in stage- specific survival. Persons surviving CRC treatment enter surveillance. For this analysis, beginning at age of 40 years, persons at higher than average risk for CRC progressed through the model for 45 one-year cycles, until age 85 years or death.

Data on age-specific CRC incidence were available for Zaragoza, one of the three provinces of Aragón, where over 70% of the people of Aragón live. In Zaragoza, the age-specific incidence of CRC from 1994 to 1998 was ~68% of the CRC incidence in the United States in the early 1990s (16, 17). During these periods, screening was not expected to have had a significant effect. It is not known whether differences in adenoma prevalence or biological behavior explain the difference in CRC incidence. To calibrate the model to reflect the average risk population of Aragón from age 50 on, we adjusted our originally published transition probabilities from normal to CRC and from large adenoma to CRC by an iterative process. Adjusting both by a factor of 0.6 yielded excellent calibration to the data from the general population of Zaragoza (Fig. 2).

Persons with a first-degree relative with CRC have approximately a 2- to 3-fold elevation in CRC risk (18). To reflect a cohort of persons with a family history of CRC in Aragón, we multiplied the general population transition probabilities from normal to small adenoma and from normal to CRC, as well as the age-specific prevalence of CRC at age 40, the age of entry into the simulation, by a conversion factor. We have previously used this approach when examining chemoprevention for persons at elevated risk of CRC (19). Making this factor equal to 3 yielded a shift in the curve of CRC incidence toward earlier ages, with age-specific increases in CRC incidence of 2.2-fold compared with the general population of Zaragoza (Fig. 2). This increase is consistent with available data on the CRC risk in persons with a first-degree relative with CRC (18). The final transition probabilities used in the model are shown in Table 1.

Data on CRC mortality rates were available for Aragón (16). In 1996, the ratio of CRC mortality to incidence was

**Table 1.** Inputs in the cost-effectiveness model

| Variable | Base case value | References |
|---|---|---|
| Clinical | | |
| Polyp prevalence at age 40, %* | 10 | (44-46) |
| Small polyp, %* | 95 | (46-48) |
| Large polyp, %* | 5 | (46-48) |
| Annual transition rate to small polyp from normal, %* | Age specific, 1.7-5.7 | (16, 18, 44-48) |
| Annual transition rate to large polyp from small polyp, %* | 1.5 | (46-49) |
| Annual transition rate to cancer without polypoid precursor, %* | Age specific, 0.0025-0.16 | (16, 18, 28, 44-46, 50) |
| Annual transition rate to cancer from large polyp, %* | 3 | (16, 17, 28, 44-46) |
| Symptomatic presentation of localized cancer, %* | 22/y over 2 y | (17) |
| Symptomatic presentation of regional cancer, %* | 40/y over 2 y | (17) |
| Mortality rate from treated localized cancer, %† | 3.3/y in first 5 y | (16, 17) |
| Mortality rate from treated regional caner, %† | 16.3/y in first 5 y | (16, 17) |
| Mean survival from distant cancer, y | 1.9 | (17, 51-57) |
| Mortality rate from cancer treatment, % | 2 | (28, 58) |
| Colonoscopy sensitivity for cancer, % | 95 | (28, 58-61) |
| Colonoscopy sensitivity for large polyp, % | 90 | (28, 58-61) |
| Colonoscopy sensitivity for small polyp, % | 85 | (28, 58-61) |
| Colonoscopy major complication rate, % | 0.1 | (28, 58, 62-67) |
| Colonoscopy mortality rate, % | 0.01 | (28, 58, 67, 68) |
| Costs | | |
| Colonoscopy | 70 euros | ‡ |
| Colonoscopy with lesion removal | 140 euros | ‡ |
| Endoscopy complication | 6,300 euros | ‡ |
| CRC care by stage | | |
| Localized | 12,300 euros | ‡ |
| Regional | 37,600 euros | ‡ |
| Distant | 55,900 euros | ‡ |

*Derived from epidemiologic and autopsy data.
†The annual mortality rate applies to those surviving to the beginning of each year, reflecting exponential decay, because the fraction of persons surviving decreases at a rate proportional to its value.
‡Derived by aggregating microcosts provided by the financial department of the Hospital Clinico Lozano Blesa, Zaragoza, Aragón, Spain.

0.52 for men and 0.48 for women (16). Therefore, the annual mortality rates after a diagnosis of localized or regional CRC were adjusted to yield an ultimate overall disease-related mortality rate of 0.5 after CRC diagnosis. Age-specific annual non-CRC mortality rates reflect epidemiologic data for Aragón (16).

***Screening strategies and surveillance.*** We compared natural history, colonoscopy every 5 years, and colonoscopy every 10 years. Screening was done from age 40 through age 80 years. Screening strategies were superimposed on the natural history model. After age 80, colonoscopy was done only to evaluate symptoms.

With colonoscopy, polyps were removed and CRCs were biopsied if detected. Test performance characteristics are presented in Table 1. With screening, CRC was managed, and symptomatic CRC could be detected, as in the natural history model. In all strategies, after adenoma detection, patients underwent surveillance colonoscopy every 5 years. Recent guidelines recommend surveillance in 3 years after removal of multiple or advanced adenomas and in 5 to 10 years after removal of one to two small adenomas (7). We selected an average interval of 5 years as a reasonable reflection of colonoscopy utilization during surveillance. Persons developing CRC underwent colonoscopy at diagnosis, 3 years later and then every 5 years thereafter (20).

The effectiveness of colonoscopy in reducing CRC incidence and mortality was not a model input defined *a priori*. It was a result of the modeling exercise, determined by the natural history parameters and the superimposed test performance characteristics of colonoscopy. In sensitivity analyses, we varied the test performance characteristics of colonoscopy to achieve less impressive CRC reduction with colonoscopy, reflecting the results of recent retrospective studies (21, 22).

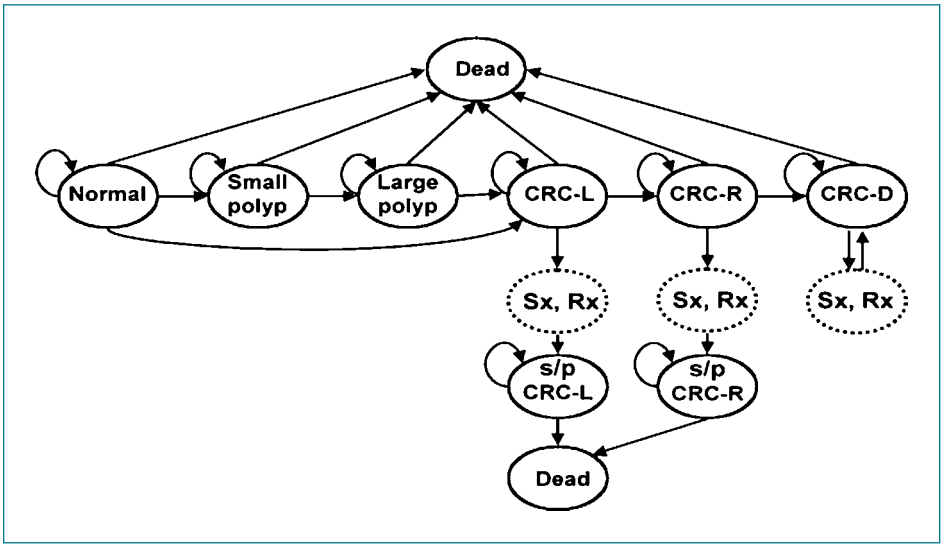


Figure 1. Markov states in the natural history model. Persons cycle between states every year from age 40 to 85. Screening colonoscopy strategies were superimposed on the natural history model.

*Cost inputs.* Costs were in year 2007 euros and reflected the relevant direct medical costs in Aragón. No published region-wide estimates were available. Therefore, we derived local cost estimates in close collaboration with the financial department of the Hospital Clinico Lozano Blesa, Zaragoza, Aragón, Spain. Procedure cost estimates were obtained by aggregating microcosts for endoscopist and nurse staffing, sedation, disposable equipment, colonoscope processing, biopsy processing and interpretation, administrative costs, and equipment cost amortization. Aggregate complication cost estimates for bleeding and perforation were obtained from the same local source. Average stage-specific total costs of care for CRC were obtained by aggregating microcosts for consultations, hospitalizations, chemotherapy, radiotherapy, surgery, and tests. The details of the cost input derivation are presented in Appendix A. We used the perspective of the regional government as the payer for direct medical costs. Because of the inherent uncertainty in the base case estimates, costs were varied in sensitivity analyses.

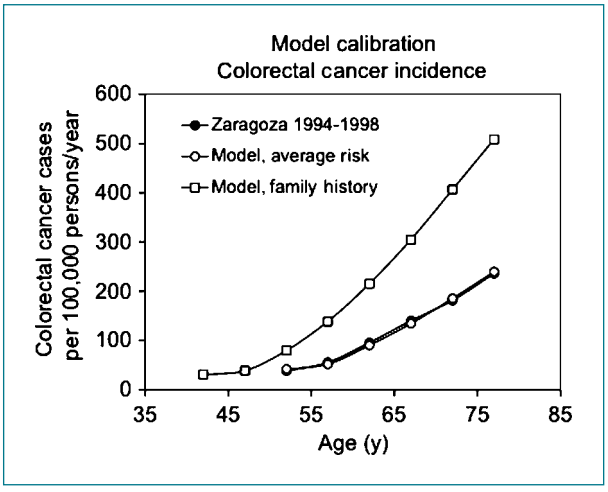


Figure 2. Model calibration for CRC incidence in Aragón, Spain.

### Clinical and economic outcomes

For each strategy, we determined CRC cases by stage, deaths by cause, and average life years and costs per person (both discounted at 3% annually; ref. 23).

### Cost-effectiveness of screening strategies

If one strategy afforded more life years than another at higher expense, an incremental cost-effectiveness ratio was calculated. Sensitivity analyses were done on model inputs.

### Annual budget impact and resources demand in Aragón

We estimated the budget impact in Aragón based on the population size reflected in year 2004 census data. A family history of CRC is reported by ~5%–11% of the general population (24, 25). We assumed that 8% of the population of Aragón from ages 40 to 80 years had a family history of CRC and were enrolled in a program of screening colonoscopy. We estimated steady-state costs for this program and annual demand for colonoscopy services as previously described for national projections in the United States (10). We first made estimates considering only costs related to CRC screening, testing, complications, and cancer care. We also made estimates, taking into consideration the average annual cost of medical care in Spain (26).

## Results

According to census data, there were 18,516 persons of age 40 years living in Aragón in 2004. If 8% of these

persons had a family history of CRC, then ~1,500 persons would be eligible to enter the screening program at age 40 years. We present base case results for a cohort size of 1,000 persons.

### Base case: Clinical outcomes

Under natural history, a cohort of 1,000 persons with a family history of CRC experienced 88 CRCs from age 40 to 85 years. Screening colonoscopy reduced this by 72% to 77% and shifted the stage at diagnosis toward earlier stages (Table 2). The fraction of deaths attributable to CRC decreased from 7.3% under natural history to 1.1% to 1.5% with screening, with accompanying improvements in discounted average life-expectancy (Table 2).

### Base case: Economic outcomes

Screening colonoscopy every 10 or 5 years both resulted in cost savings compared with natural history (Table 2). Under natural history, 99% of the total cost was for care of CRC (Fig. 3). Screening costs accounted for 52% of total costs with colonoscopy every 10 years, and 66% of costs with colonoscopy every 5 years, whereas cancer care costs decreased substantially to 44% and 30% of total costs for the two screening strategies, respectively (Fig. 3). The relatively high cost of CRC care compared with screening in Aragón (Table 1) accounts for the result that screening was cost-saving overall in the base case.

### Base case: Cost-effectiveness

Because each screening strategy was both more effective and less costly than natural history, the screening strategies were dominant over natural history. Colonoscopy every 5 years afforded an incremental increase in discounted life expectancy compared with colonoscopy every 10 years at an acceptable cost, with an incremental cost-effectiveness ratio of 7,250 euros per life year gained (Table 2).

### Base case: Budget impact and resources demand

According to the 2004 census, 624,067 of the 1,249,584 persons living in Aragón were 40 to 85 years of age. Assuming that 49,925 (8%) of these persons had a family history of CRC and participated in a screening program, and assuming a steady-state population size, screening was expected to decrease annual CRC incidence in these persons with accompanying overall cost savings per year (Table 3). Colonoscopy demand increased substantially with the screening strategies, as expected. Demand for colonoscopy with the strategy of screening every 10 years was ~70% of that with screening every 5 years (Table 3). This fraction is higher than 50% because those persons diagnosed with adenomas were enrolled in surveillance.

The estimates in Table 3 do not take into account the costs of establishing and operating a screening program. However, based on the cost savings, an estimated 1,820,000 to 1,950,000 euros per year (36-39 euros per person per year) could be allocated toward these purposes while maintaining a neutral budget.

### Sensitivity analyses

The effect of varying the model's inputs is shown in Table 4. The cost of screening had the greatest effect on the results. If the costs of colonoscopy without and

**Table 2.** Base case clinical and economic results and incremental cost-effectiveness ratios

| | Natural history | Screening colonoscopy every 10 y | Screening colonoscopy every 5 y |
|---|---|---|---|
| CRC cases per 1,000 persons from age 40 to 85 years | 88 | 24 | 20 |
| Reduction in CRC incidence compared with natural history | | 72% | 77% |
| CRC stage | | | |
| Localized | 35 (40%) | 15 (60%) | 13 (65%) |
| Regional | 33 (37%) | 7 (30%) | 6 (29%) |
| Distant | 20 (23%) | 2 (9%) | 1 (7%) |
| Deaths attributable to CRC | 7.3% | 1.5% | 1.1% |
| Life years per person* | 22.382 | 22.499 | 22.508 |
| Cost per person* | 1,118 euros | 589 euros | 656 euros |
| Increment cost per life years gained compared with | | | |
| Natural history | — | Dominates† | Dominates† |
| Screening colonoscopy every 10 y | — | — | 7,250 euros |

*Discounted at 3% per year.

†Strategy in top row is more effective and less costly than strategy in left column to which it is being compared.

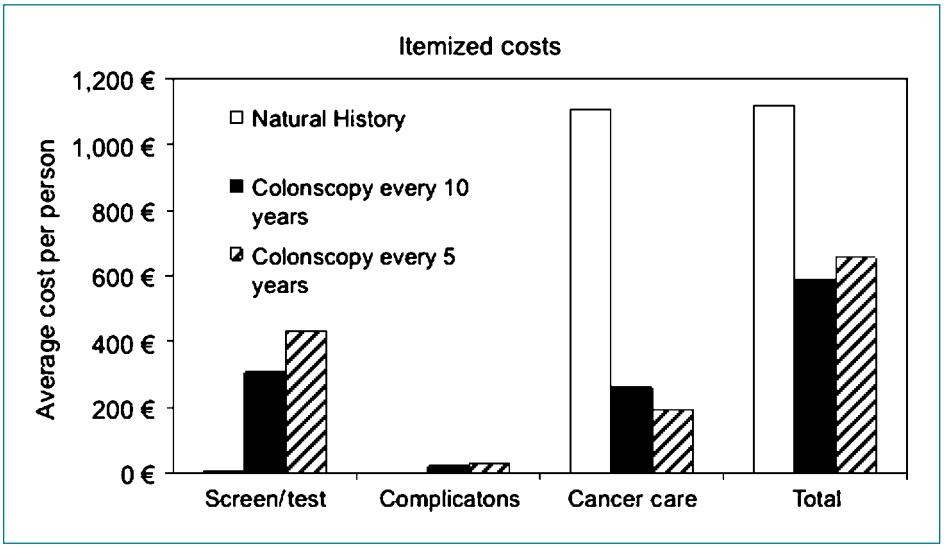


**Figure 3.** Itemized costs for natural history and screening strategies.

with polypectomy both doubled compared with the base case, screening no longer dominated natural history. Screening colonoscopy was very cost-effective compared with natural history under this scenario, but screening every 5 years compared with every 10 years began to become costly (incremental 34,800 euros per life year gained). With a 5-fold increase in screening costs, screening remained very cost-effective, but screening every 5 years compared with every 10 years cost an incremental 62,100 euros per life year gained.

As the level of CRC risk in the screened cohort compared with the risk of the general population increased to 3-fold and 4-fold elevations, which are reflective of family histories of two and three first-degree relatives with CRC, respectively, screening gained more life years in the cohort while remaining dominant over no screening, and the cost-effectiveness of screening every 5 years compared with every 10 years improved (Table 4). Even at only a 2-fold risk compared with the general population, screening colonoscopy every 5 years remained cost-effective. The cost-effectiveness of screening improved as the costs of CRC care increased.

Changes in the individual variables for sensitivity of colonoscopy for polyps or CRC and the rate and cost of colonoscopy complications had minimal effect on the results (Table 4). In a scenario reflecting less optimistic overall benefit from screening colonoscopy, we adjusted the sensitivities of colonoscopy to yield CRC incidence reduction of ~50% with screening every 10 years and ~65% with screening every 5 years compared with natural history. With these assumptions, screening remained cost saving compared with natural history, and screening every 5 years dominated screening every 10 years, reflecting the higher relative cost of CRC treatment compared with screening (Table 4). With the base case assumptions and at an extreme mortality risk from colonoscopy (one death in 2,000), screening still dominated natural history, but the risk

**Table 3.** Base case annual budget effect and endoscopic resources demand

| | Natural history | Screening colonoscopy every 10 y | Screening colonoscopy every 5 y |
|---|---|---|---|
| Annual no. CRC cases diagnosed | 114 | 31 | 26 |
| Total cost (only CRC testing, screening, complications and cancer care) | 3,360,000 euros | 1,451,000 euros | 1,539,000 euros |
| Total cost (including general average annual medical costs in Spain)* | 62,407,000 euros | 60,453,000 euros | 60,539,000 euros |
| No. colonoscopies per year | 275 | 7,360 | 10,334 |

NOTE: Assuming steady-state cohort size of 49,925 persons (8% of the 624,067 persons of age 40 to 85 y living in Aragón, according to 2004 census data).
*Assuming average annual cost of 1,200 euros per person for care not related to CRC.

**Table 4.** One-way sensitivity analyses

| Subject of sensitivity analysis | Base case value(s) | Value(s) in sensitivity analysis | Colonoscopy every 10 y versus natural history | | Colonoscopy every 5 y versus natural history | | Colonoscopy every 5 y versus colonoscopy every 10 y | |
|---|---|---|---|---|---|---|---|---|
| | | | Life years gained per 1,000 persons | Cost per life year gained | Life years gained per 1,000 persons | Cost per life year gained | Life years gained per 1,000 persons | Cost per life year gained |
| CRC risk compared with general population of Zaragoza | 2.2-fold | 2-fold | 107 | Dominates | 115 | Dominates | 8 | 9,780 euros |
| | | 3-fold | 150 | Dominates | 164 | Dominates | 14 | 2,800 euros |
| | | 4-fold | 190 | Dominates | 209 | Dominates | 19 | 753 euros |
| Colonoscopy Sensitivity for CRC | 95% | 90% | 116 | Dominates | 125 | Dominates | 9 | 7,240 euros |
| | | 97% | 117 | Dominates | 126 | Dominates | 9 | 7,260 euros |
| Sensitivity for large polyp | 90% | 85% | 115 | Dominates | 125 | Dominates | 10 | 6,120 euros |
| | | 95% | 118 | Dominates | 127 | Dominates | 8 | 8,590 euros |
| Sensitivity for small polyp | 85% | 80% | 115 | Dominates | 125 | Dominates | 10 | 6,140 euros |
| | | 90% | 118 | Dominates | 126 | Dominates | 8 | 8,570 euros |
| Probability of complication | 0.1% | 0.05% | 117 | Dominates | 126 | Dominates | 9 | 6,740 euros |
| | | 0.5% | 117 | Dominates | 126 | Dominates | 9 | 11,350 euros |
| Probability of death related to colonoscopy | 0.01% | 0.005% | 119 | Dominates | 130 | Dominates | 11 | 6,340 euros |
| | | 0.05% | 95 | Dominates | 93 | Dominates | −1.3 | Dominated |
| Cost (diagnostic/ with lesion removal) | 70 euros/ 140 euros | 210 euros/ 420 euros | 117 | 820 euros | 126 | 3,320 euros | 9 | 34,800 euros |
| | | 350 euros/ 700 euros | 117 | 6,140 euros | 126 | 10,300 euros | 9 | 62,100 euros |
| Cost of complication | 6,300 euros | 4,000 euros | 117 | Dominates | 126 | Dominates | 9 | 7,200 euros |
| | | 12,000 euros | 117 | Dominates | 126 | Dominates | 9 | 8,180 euros |
| CRC incidence reduction with screening every 10 y/screening every 5 y | Base case inputs yield reductions of 72%/77% | Colonoscopy sensitivities adjusted to yield reductions of 52%/65% | 87 | Dominates | 109 | Dominates | 22 | Dominates |
| CRC care costs Localized/ regional/distant | 12,300 euros/ 37,600 euros/ 55,900 euros | 6,150 euros/18,800 euros/27,950 euros | 117 | Dominates | 126 | Dominates | 9 | 8,680 euros |
| | | 24,600 euros/75,200 euros/111,800 euros | 117 | Dominates | 126 | Dominates | 9 | 4,320 euros |

NOTE: "Dominates" denotes situation where first strategy is more effective and less costly than second strategy. "Dominated" denotes situation where first strategy is less effective and more costly than second strategy.

of colonoscopy every 5 years compared with every 10 years outweighed the benefit.

### Impact of clinical and modeling results on regional planning and budget decisions in Aragón

A major component of the CRC prevention pilot program of Aragón has focused on first-degree relatives of patients with CRC. First-degree relatives are contacted by a nurse and are referred to a high-risk clinic where a doctor explains the purpose of screening and the potential benefits and risks. If a patient accepts, a colonoscopy is scheduled. First-degree relatives can obtain additional information in a specific web site (27) and can ask further questions by telephone. This is accomplished with a limited budget of ~80,000 euros per year, provided that doctors and nurses belong to the public health system and colonoscopies are done within the public health system.

The preliminary clinical results for the prevention program and the decision analytic modeling results were presented to regional health authorities in January 2009. In summary, 2,657 families had been contacted to participate by January 2009 and 1,863 40-year-old or older first-degree relatives of persons with CRC had undergone at least one colonoscopy. One in five first-degree relatives had at least one adenoma, and one in 62 had CRC (either *in situ* or more advanced).

In consideration of the clinical experience and our modeling results and in celebration of European Colorectal Cancer Month, the health authorities of the Autonomous Region of Aragón decided on March of 2009 to expand the current pilot CRC screening program to all health sectors of the region of Aragón.

## Discussion

This study shows how a validated decision analytic model can be tailored to reflect a specific regional scenario to inform public policy decisions. The results of our analysis suggest that screening first-degree relatives of patients with CRC is likely to be highly cost-effective and perhaps even cost saving in Aragón, Spain, given local cost structures.

Our study's results must be viewed in the context of previous studies addressing the cost-effectiveness of CRC screening. Multiple studies examining various strategies, including FOBT, flexible sigmoidoscopy, colonoscopy, and computed tomographic colonography suggest that CRC screening is cost-effective (10, 11, 28-39). The cost-effectiveness of CRC screening has usually been studied in theoretical average risk populations. No single screening strategy has emerged as uniformly superior across all studies in average risk persons. In a limited number of scenarios, studies have found screening to be cost saving, including scenarios with relatively low screening costs (40, 41) and relatively high CRC treatment costs (41). Previous studies have highlighted specific national scenarios (10, 38) and the appropriateness of the indication for colonoscopy (36). A prior study focusing on persons with a family history of CRC reported that higher intensity screening starting at earlier age seems cost-effective in persons with a family history of CRC (39), findings that are similar to ours.

In this study, we examined a specific prevention program in Aragón, Spain, focused on first-degree relatives of persons with CRC. Our modeling results suggest that, in this population, CRC screening may substantially decrease the burden of CRC and may actually be cost saving due to the relatively low local costs of screening compared with the costs of cancer care. As the number of affected first-degree relatives increased to 2 or 3, representing ~3-fold and 4-fold elevations in CRC risk compared with the general population (42), the cost-effectiveness of intensive screening improved. Under a less optimistic scenario designed to reflect the results of recent studies about the protective effect of colonoscopy (21, 22), colonoscopic screening remained dominant over natural history, and screening every 5 years dominated screening every 10 years. These results reflect the much larger economic costs of CRC treatment relative to the costs of screening in our study scenario.

Guidelines recommend colonoscopy every 10 years when the affected first-degree relative is diagnosed with CRC at age 60 years or older and every 5 years if the age at diagnosis is age 60 years or younger or if two or more first-degree relatives are affected (7). Our results suggest that colonoscopy every 5 years could be considered cost-effective by traditional standards compared with colonoscopy every 10 years even with only a 2-fold elevation in CRC risk compared with the general population. This strategy would require significantly more colonoscopies per year than a strategy with a 10-year interval. At present, we do not know whether the number of colonoscopies required with such a strategy could be delivered in Aragón or how this more intensive program might affect participation rates.

Our study exemplifies how the results of decision analytic modeling can compliment information from published epidemiologic studies and clinical trials, as well as local experience, and contribute to regional policy decision-making. The CRC prevention program in Aragón focusing on high-risk individuals has been in continuous development since 2002, when it started as a pilot screening program. In addition to screening first-degree relatives of persons with CRC, it also aims to identify families with very high risk due to genetic syndromes. Since its inception, institutional support has included direct budget allocation for genetic testing, database development and maintenance, internet-based resources, and personnel including data managers and part-time nurses. Support has also been essential to allow use of public endoscopy facilities and participation by endoscopy personnel. The pilot program for high-risk persons was developed based on published

guidelines and thus included colonoscopy as the test of choice and a starting age of 40 or 10 years earlier than the age of CRC diagnosis in a relative. The decision to expand the program was supported by published literature, the promising results of the program in those centers where it was fully implemented, and the projected benefits suggested by our decision analysis.

Additional CRC screening efforts have also been launched in Aragón. According to European legislation, all countries of the European Community should have a CRC screening program or, at least, a pilot study as of 2008 (43). In March 2009, coinciding with the decision to expand the high-risk screening program, the regional health authorities in Aragón decided to launch a pilot CRC screening program in average risk individuals based on biennial immunologic FOBT starting at age 50, consistent with existing guidelines. The regional implications of a screening program in average risk persons have yet to be defined. Our experience with the high-risk program shows how local decision making may be influenced by the results of the pilot program itself and the results of decision analytic modeling tailored to regional considerations.

In Spain, looking beyond Aragón, an important future challenge is the expansion of CRC control efforts nationwide. We believe that establishing programs similar to ours elsewhere in Spain should be attainable. The costs for endoscopy and cancer are very similar among the different autonomous regions of Spain and the National Health Service covers >80% of the population. We recognize that our clinical experience and the results of this modeling study may not be applicable in other countries with private or mixed (private and public) health systems or with different cost structures. However, this may serve as an instructive case study for other countries or communities where the public system is the major care provider. It remains to be seen to what extent our regional results affect decision making at the national level in Spain.

Our study has several limitations. First, a variety of combinations of transition probabilities between states could produce a model calibrated to the CRC incidence observed in Zaragoza, but the combination that most reflects reality is not known. When family history is taken in consideration, it is not known if CRC progression rates are similar to those assumed for an average-risk population. Second, our model does not consider specific patient subpopulations separately depending on the specific CRC burden in the family. Nonetheless, in sensitivity analyses, we explored a range of CRC risk and found that screening was still quite effective and cost-effective even at the lower end of risk elevation compared with average-risk persons. Third, we did not model families with genetic syndromes such as Lynch syndrome, who are another focus of the prevention program for high-risk persons. Fourth, the actual effect of the program will depend on uptake and adherence rates. Our results provide infor mative upper bound estimates for regional health authorities and other decision makers. Fifth, recent studies suggest that colonoscopy may be effective in reducing CRC incidence primarily in the left colon and not the right colon (21, 22), and our model is not designed to examine the location of lesions in the colon. Finally, our estimates are based on a steady-state population size. Although population size has been stable over time in Aragón, population growth will affect the global estimates.

In conclusion, our decision analysis suggests that colonoscopic screening of first-degree relatives of persons with CRC in Spain is likely to provide significant clinical benefit at acceptable costs, assuming Aragón is reflective of the country as a whole. Depending on local cost structures, screening could even be cost saving, resulting in no adverse effect on overall regional budgets. Our study illustrates how decision analytic modeling that is tailored to regional clinical, epidemiologc, and economic realities can inform regional public policy decisions.

## Appendix A. Derivation of Cost Inputs

### 1. Cancer care costs

Itemized average cancer care costs per person in year 2004

| Stage | Cost excluding chemotherapy and radiotherapy, in year 2004 (in euro) | Approximate average chemotherapy costs, in year 2004 (in euro) | Average radiation therapy costs (2,388 euro per patient treated), in year 2004* (in euro) |
|---|---|---|---|
| A | 2,675 | | |
| B | 12,461 | 6,500 | 366 |
| C | 15,292 | 10,000 | 549 |
| D | 17,624 | 33,000 | 549 |

*In 2005 in Spain, 23% of CRC cases were rectal cancer cases.

From above, the following inputs were calculated and updated 3% per year to 2007. Total average cancer care costs/person in year 2007 euros

| Stage | Total cancer cost in euro |
|---|---|
| Localized | 12,300 |
| Regional | 37,600 |
| Disseminated | 55,900 |

Assuming half of stage B are categorized as localized and half as regional.

**2. Colonoscopy complication costs**

| | |
|---|---|
| Bleeding/hospitalization | 2,356 euros |
| Bleeding/hospitalization/surgery | 5,980 euros |
| Perforation | 10,510 euros |

Average cost per complication

| | |
|---|---|
| Complication cost | 6,300 euros |

Assuming 2/3 bleeding and 1/3 perforation; 1/2 bleeding require surgery.

**3. Colonoscopy costs**

| | |
|---|---|
| Colonoscopy | 70 euros |
| Colonoscopy with biopsy | 140 euros |

Itemized costs of colonoscopy with biopsy (in euro)

| | |
|---|---|
| Endoscopist | 27.23 |
| Nurse | 17.38 |
| Nurse assistant | 1.41 |
| Nurse anesthetist | 1.38 |
| Administrative assistant | 1.41 |
| Purge solution | 4.64 |
| Absorbent pad | 0.17 |
| Distilled water | 1.08 |
| Suction bag | 1.12 |
| Venous canula | 0.43 |
| Gauze, first 4 | 0.04 |
| Gauze, additional | 0.06 |
| Gloves | 0.02 |
| Syringe | 0.05 |
| Stopcock | 0.20 |
| Lubricant | 0.34 |
| Saline | 0.11 |
| Formaldehyde | 0.04 |
| Tubing | 0.01 |
| Dye | 1.70 |
| Biopsy forceps | 16.58 |
| Snare | 17.25 |
| Fentanyl | 0.30 |
| Midazolam | 0.23 |
| Propofol | 7.39 |
| Detergent | 0.97 |
| Disinfectant | 2.41 |
| Cleansing liquid | 1.44 |
| Colonoscope amortization | 2.16 |
| Light source amortization | 1.17 |
| Processor amortization | 1.75 |
| Cautery equipment amortization | 0.90 |
| Bed amortization | 0.25 |
| Monitor amortization | 0.43 |
| Cleaning equipment amortization | 0.37 |
| Biopsy | 20.00 |

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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