



UNIVERSIDADE CATÓLICA PORTUGUESA

Cost-effectiveness of colorectal screening in Portugal

Was biennial FIT a good choice?

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COST-EFFECTIVENESS OF COLORECTAL SCREENING IN PORTUGAL – WAS
BIENNIAL FIT A GOOD CHOICE?

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Resumo

A avaliação económica é cada vez mais utilizada pelos vários sistemas de saúde para apoiar decisões sobre quais as tecnologias de saúde a financiar com os recursos limitados disponíveis. O desenho e implementação do programa de rastreio do cancro colo-rectal (CCR) em Portugal, utilizando como teste de rastreio, o teste imunoquímico fecal (FIT) bianual não foi suportado por nenhum estudo custo-eficácia conhecido, na perspetiva do Serviço Nacional de Saúde (SNS), usando dados específicos do país. Neste trabalho pretendemos determinar a estratégia mais custo-eficaz para o rastreio do CCR em Portugal. Foi desenvolvido um modelo de Markov para simular a história natural do CCR e avaliar a relação custo-eficácia de cinco estratégias de rastreio, bem como do não rastreio, em indivíduos com 50 anos de idade com risco médio de CCR. O outcome primário é a razão de custo-efetividade incremental (ICER) entre as diferentes estratégias de rastreio.

A colonoscopia 3/10 anos é a estratégia mais custo-eficaz para o rastreio do CCR em Portugal, com um ICER de 802,07€ por QALY em comparação com a colonoscopia a cada 10 anos. As estratégias baseadas em testes de sangue oculto nas fezes e a colonografia por TC são mais caras e menos eficazes do que as estratégias baseadas em colonoscopia para o rastreio do CCR. A FIT bianual é a estratégia com os menos anos de vida ganhos (LYG) (498.3 dias) de todas as estratégias, bem como a que apresenta menor diminuição da incidência de CRC (-37%) e a menor redução na mortalidade por CCR (-57 %) num cenário de aderência realista.

De acordo com os nossos resultados, a FIT bianual, a estratégia de rastreio utilizada em Portugal, deve ser abandonada por ser a estratégia mais cara e

menos eficaz para o SNS, e substituída por uma das duas estratégias baseadas na colonoscopia.

Palavras-chave: custo-eficácia, ICER, rastreio, cancro colo rectal, avaliação económica em saúde

Abstract

Economic evaluation is increasingly used by various health care systems to support decisions about which health technologies to fund with the limited resources available. The design and implementation of the Portuguese colorectal cancer (CCR) screening program, using biennial fecal immunochemical test (FIT 2/2y) was not supported by any published cost-effective analysis using country-specific data from a payer's perspective. We aim to estimate the most cost-effective strategy for CCR screening in Portugal. A Markov model was developed to simulate the natural history of colorectal cancer and to estimate the cost-effectiveness of five strategies for CRC screening, as well as no screening, in 50-year-old individuals at average risk for colorectal cancer. The primary outcome was the incremental cost-effectiveness ratio (ICER) between the different screening strategies.

Colonoscopy 3/10 years is the most cost-effective strategy for colorectal screening in Portugal, with a cost-effectiveness ratio (ICER) of 802,07€ per QALY compared with colonoscopy every 10 years. The stool based strategies and CT colonography strategies are more expensive and less effective than colonoscopy based strategies for CCR screening. FIT 2/2 y showed the smallest gains in life years gained (LYG) (498.3 days) of all strategies, as well as the smallest reduction in the incidence of CRC (-37%) and the smallest reduction in CCR mortality (-57%) under real-world adherence assumptions.

According to our results, biennial FIT, the screening strategy used in Portugal, should be abandoned as it is the most expensive and less effective strategy for the NHS, and replaced by one of the two colonoscopy strategies.

Keywords: cost-effectiveness, ICER, screening, colorectal cancer, economic modelling

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Introduction

There is a large gap between the choice, formulation and implementation of health policies, and the evidence that sustains its design and potential impact vis-à-vis other alternative policies, particularly in public health (Gautam, 2017). Not infrequently, the assessment of their impact is performed after their actual implementation. In several situations the policies are implemented, without a clear strategical blueprint, as a reactive response to contingent political/public pressures, without a prior evaluation that appraised the impact of the policies under different scenarios.

Economic evaluation is increasingly used by various health care systems to support decisions about which health technologies to fund with the limited resources available. The term “technology” should be interpreted broadly, covering not only new drugs and new devices, but also screening programs among others.

Cost-effective analysis (CEA) is the most common health technology assessment (HTA) type of analysis performed. In CEA costs and health benefits from different alternatives are compared, and after rejecting the alternatives that are more costly and less effective (dominated alternatives), incremental cost-effectiveness ratios (ICERs) are obtained. The ICER is the ratio of the difference in costs to the difference in outcomes, indicating how much expensive is providing a health improvement in monetary terms.

A health screening program have the enormous potential to improve public health outcomes and improve universal health coverage. When well organized, they can prevent disease, reduce disability and reduce mortality. There are countless examples of screening programs implemented around the world, for various conditions, such as colorectal cancer, breast cancer, antenatal screening, diabetic retinopathy, among others. A screening program is not just a single test but rather a pathway that begins with selecting people who are eligible for screening and ends when the outcomes are observed (Organization, 2020).

The decision to implement a screening program in a country is complex, and must take into account several dimensions, such as, evidence of cost-effectiveness, feasibility, stakeholder support, and being part of a country's public health priorities. An important step in the decision to start a screening program is to carry out a CEA across different alternatives, using country-specific inputs. In Sweden, as an example, the decision pathway for implementing a screening program is a well-organized process, with 15 evaluation criteria, a defined organization and systematic work process, which takes approximately two years to complete (Organization, 2020).

Colorectal cancer [CRC] is a major cause of cancer-associated morbidity and mortality worldwide and the 3rd leading cause of cancer-related death in Portugal (Bray et al., 2018). Screening for CRC reduces mortality by: (1) detection of early-stage cancers and (2) detection and removal of benign precursor lesions, i.e. adenomas. Several screening methods are available: fecal occult-blood test (FOBT), fecal immunochemical test (FIT), flexible sigmoidoscopy, total colonoscopy, CT-colonography and stool DNA testing. CCR screening is endorsed by most health agencies, but recommendations are diverse (Wolf et al., 2018). Although the various screening methods have different levels of accuracy (colonoscopy is considered the gold-standard by most), the concept has long been that one test is better than no test at all (Rex et al., 2017).

Cost-effectiveness data for CRC screening in Europe are scarce, with diverging results, generating uncertainty about the best screening strategy and its own effectiveness. In Portugal (PT), there is an organized screening program using FIT every 2-years that targets the average-risk population, implemented in 2017 (Ministério da Saúde, 2017). The design of the Portuguese screening program was not supported by any published CE analysis modelling using country-specific data from a payer's perspective. There is only one CE study published in 2019, addressing CCR screening, using a societal perspective, not suitable for a policy decision on screening implementation due to lack of consistency and objectivity (Areia et al., 2019).

The Portuguese NHS spends a large amount of money subsidizing FIT and colonoscopy, the major tests used in the CRC screening program, offered for free or at a very low cost (subsidized by the NHS), by a large network of private health care units. Since April 2014, Portugal is one of the few developed countries in which anesthesia assisted colonoscopy performed by anesthesiologists is available, in an open-access model, requested by the primary care physician, almost free at the point-of-service. In 2018, about 500 000 colonoscopies were performed in Portugal, being the larger share financed by the Portuguese NHS.

Given this context of uncertainty and multiple paths, a cost-effectiveness model is highly recommended to support the political decision for CRC screening.

We aim to estimate the most cost-effective strategy for CCR screening in Portugal.

Chapter 1 – Literature review

1.1 Colorectal cancer and screening

1.1.1 Epidemiology

Colorectal cancer represents the third most common cancer in the world, comprising around 10% of all cancer diagnoses (Bray et al., 2018; Rawla et al., 2019). In 2018, 1.8 million new cases of CRC have been diagnosed, more commonly in older people (most patients were over 60 years at the time of diagnosis). In general, it is more common among men (1,026,215 vs. 823 303), and 3 to 4 times more frequently in developed countries (Bray et al., 2018). Concerning mortality, it is the second leading cause of cancer death worldwide corresponding to 9% of all cancer deaths (Bray et al., 2018).

In Europe, colorectal cancer represents both the third most common cancer site and death from cancer (Ferlay et al., 2018), with an estimated 380,000 new cases and 175,000 related deaths in 2018 (Bray et al., 2018).

In 2018, Portugal reported 10,270 estimated new cases of colorectal cancer (17.6% of the total number of new cancers) corresponding to the third most incident cancer (10.2%) and the second cause of cancer death in the country (9.2%), with 4261 estimated deaths in 2018 and about 12 years of potential life lost (Bray et al., 2018). Over 10,501 Portuguese are expected to be diagnosed with CRC in 2020. It is third leading cause of cancer death, only surpassed by lung and prostate cancers, expecting 4,320 deaths in 2020.

In contrast to the USA, the standardized incidence rate of colorectal neoplasms has been steadily increasing over the years in Portugal, in accordance to the Portuguese General Directorate of Health (Direcção Geral da Saúde, 2014). Similarly, CRC related deaths increased by 3% per year between 2000 and 2005 (Pinto et al., 2010).

1.1.2 Colorectal cancer development pathways

Colorectal cancer is thought to be the end result of a multistep process arising from an aberrant crypt that evolves into a neoplastic precursor lesion - a polyp- that will eventually progress to colorectal cancer over an estimated 10 year (Dekker et al., 2019).

Nowadays, there are three major colorectal carcinogenesis pathways documented: the traditional adenoma–carcinoma pathway (also known as the chromosomal instability sequence), responsible for 70-90% of sporadic CRC; the serrated neoplasia pathway, responsible for 10-20% of CRC; and the microsatellite instability pathway, responsible for up to 7% of sporadic CRC and for Lynch syndrome (Dekker et al., 2019; Nguyen et al., 2020).

Conventional adenomas progress by the sequential accumulation of genetic mutations and chromosomal instability leading to microsatellite stable tumors. The sessile serrated neoplasia pathway is often initiated by genetic mutation of BRAF or KRAS genes, progressing by methylation of tumor suppressing genes and leading to both microsatellite stable and unstable tumors. Defective DNA repair through inactivation of mismatch repair genes leads to microsatellite instability, seen in Lynch syndrome and less frequently in sporadic (Dekker et al., 2019).

1.1.3 Rational for screening

Organized screening programs allow an active invitation of all eligible patients, send reminders to increase compliance, as well as a thorough monitoring in the several screening stages, resulting in a higher adherence rate to subsequent follow up, comparatively to opportunistic screening (Săftoiu et al., 2020).

Screening for colorectal cancer is nowadays a Public Health priority in Europe, and Portugal makes no exception. The increasing burden of CRC, related to population growth, increasing age and lifestyle changes makes primary prevention difficult (Cotter, 2013; Rawla et al., 2019). As so, efforts to control this problem must rely largely on screening. CRC is the only cancer for which screening has been shown to reduce mortality in both average-risk men and women (Brenner et al., 2007).

Adenomatous polyps, the most relevant precursors of CRC, occur in about 30% of men and 20% of women, and the estimated interval time of progression from adenoma to carcinoma is around 10 years (Hisabe et al., 2014). The high disease incidence and slow progression of precancerous lesions, combined with and the available accurate screening tools and effective therapeutic regimes make detection of precancerous lesions and early cancer stages a goal for organized screening strategies. However, it should be kept in mind that multiple factors play a role in the effectiveness of screening: test performance, accessibility, and compliance to screening (Issa & Nouredine, 2017; Ladabaum et al., 2020).

Mortality reduction and increased survival is directly related to the stage of the disease at the time of diagnosis. As so, organized population-based screening allows the detection not only of pre-malignant lesions that can be removed, but also of early malignant lesions, amenable to treatment.

1.1.4 CCR recommended screening strategies

According to recommendations from most professional society guidelines and expert groups CRC screening programs should start at the age of 50 years in most average-risk adults, as most cancers occur over that age (Bibbins-Domingo et al., 2016; Rex et al., 2017; Săftoiu et al., 2020; Wolf et al., 2018). For average-risk African American people, some societies advocate starting screening at the age of 45 (Carethers, 2015), despite limited evidence to such recommendation. Screening should be continued until the age of 75 years for average risk patients, as long as their life expectancy is 10 years or greater (Săftoiu et al., 2020).

Despite several available strategies for CRC screening, there is no international consensus on the methodology that should be used, as human and financial resources vary across countries.

Screening strategies can be divided into three major groups: stool-based testing (hemoglobin or DNA detection), direct visualization of the colon and rectum with endoscopy and radiological imaging evaluation.

Stool-based tests include Fecal Immunochemical Test (FIT), guaiac-based Fecal Occult Blood Test (gFOBT), Multitarget stool DNA tests with fecal immunochemical testing (FIT-DNA). Nowadays, most societies advocate the use of FIT (directly measuring hemoglobin in stools), requiring only a single stool sample performed every 1 to 3 years, depending on the screening policy of each nation. Sensitivity and specificity of FIT for detecting CRC varies between 0.73-0.92 and 0.90 and 0.97, respectively (Rex et al., 2017; Wolf et al., 2018). A positive FIT requires a subsequent colonoscopy for further evaluation.

Endoscopic screening potentially allows removal of polyps and identification of early stages of CRC. Total colonoscopy is usually performed every 10 years for a patient with an average risk of CRC, showing good sensitivity (0.75-0.98) and specificity (0.89-0.94) for adenoma detection, as well as for CRC diagnosis (sensitivity for 0.97 and specificity of 1) (Aronsson et al., 2017; J. S. Lin et al.,

2016). Sigmoidoscopy is another endoscopic screening tool, performed every 5 years in average risk patients, showing an overall reduction of 21% and 28% in CRC incidence and mortality, respectively, for those offered screening (O. S. Lin et al., 2014). A positive sigmoidoscopy requires a subsequent colonoscopy to complete colonic evaluation.

Computed Tomography Colonography, performed every 5 years in average risk patients, is another screening tool, with sensitivity and specificity for adenoma detection ranging between 0.73-0.98 and 0.89-0.95, respectively (J. S. Lin et al., 2016).

The European Society of Gastrointestinal Endoscopy (ESGE) recommends organized population-based screening programs for average-risk population aged between 70-75 years old, using FIT as the main screening tool (Wolf et al., 2018). Colonoscopy or sigmoidoscopy may also be considered major screening tools, depending on medical and financial resources and adherence of the population to such screening modality.

1.1.5 CCR screening in Portugal

Since 2018, Portugal is progressively implementing an organized population-based screening program, using FIT as the primary screening test (Ministério da Saúde, 2017). Asymptomatic average risk population aged between 50-74 years are offered FIT every two years. In case of a positive FIT, patients are referred for total colonoscopy, under informed consent and within the scope of the Portugal National Health Service, in an average period of no more than 90 days (Ministério da Saúde, 2017). The referral algorithm after colonoscopy varies depending on the result of the exam and is performed based on the recommendations of the ESGE. In cases where colonoscopy is normal or presents findings that do not require early surveillance, it must be repeated 10 years later, and FIT testing should be suspended for at least for five years after (Săftoiu et al., 2020).

In 2016/2017 the Northern Regional Health Administration (ARS Norte) launched a pilot project for CRC screening of 6 000 people from 10 Family Health Units in Valongo, Maia, Póvoa de Varzim and Vila do Conde. Patients were recruited for the project through a personalized invitation made by General Practitioners or through an invitation letter sent to the patients' homes. Since 2017, invitation letters and a container for stool sample collection have been sent to patient's homes, to perform FIT every two years.

Similarly, the Algarve Regional Health Administration (ARS Algarve), implemented a pilot population-based CRC screening program in September 2017, to average-risk population aged 50-75 years, by performing FIT every two years. All FIT-positive patients were invited to undergo a total colonoscopy.

Preliminary results (2017-2019) of the Algarve pilot program showed that 34.4% (n=8594) of the target population (n=25,017) agreed to participate, 27.5% (n=6883) were submitted stool sample for analysis, with a 3.9% (n=266) of positive FIT. These patients were invited to perform a total colonoscopy, with a 57.5% (n=153) adherence rate: six patients had carcinoma and 685 had adenomas (Correia et al., 2019)

1.1.6 – Clinical Trials and Modeling Studies

Randomized clinical trials (RCT) are considered as providing the highest quality of evidence in Medicine as they prevent any bias from confounding variables or selective allocation (Brenner Hermann., Cross, 2021).

However, we have to be aware that RCTs have some important limitations, as the main source of evidence for screening programs with long term outcomes. First, it requires a large number of participants (as the CRC mortality in the population is relatively low) and, given the slow development of most CRCs, a very long follow-up period (at least 10 years). Typically, it takes between 15-20 years from the RCT design until main results are available (Brenner Hermann.,

Cross, 2021). Second, RCTs generally compare 2 (at most 3) screening strategies, with very precise specifications, such as screening intervals, target population age range, FIT threshold, among others. As such, a single RCT will usually provide comparison between just two screening strategies with the specifications used.

In CCR screening, the evidence obtained from RCT, although important is clearly insufficient, as it is no feasible to compare so many different screening options with long-term outcomes (Brenner Hermann., Cross, 2021; Wolf et al., 2018). Given these limitations decision analytical models have been used to compare the effectiveness of multiple screening strategies, using data from multiple sources, including RCT and observational studies(Heisser et al., 2020). In screening for CCR, the most appropriate source of evidence for decisions will likely come from modelling studies rather RCTs.

It allows to compare all relevant alternatives, combining information from RCT and other studies, project beyond the time horizon of a RCT (as RCT seldom capture the patient's lifetime), and include particular setting or group of patients not included in RCT. Modeling has its own limitations, as it is always a simplification of the real world.

1.2 Economic evaluation in health care

Economic evaluation is increasingly used to assess the decisions in various health care systems about which health care technology to fund given the available resources. This health care technologies could involve coverage or reimbursement of new pharmaceuticals, expensive technologies, implementation of large scale health interventions, such as population screening for certain diseases, among others.

The first countries to use economic evaluation were the public health systems from Australia and Ontario, Canada (Briggs et al., 2006). Economic evaluation means the comparison of alternative options in a specific technology in terms of their costs and outcomes (Weinstein et al., 1996b). Options mean alternative ways in which health resources can be used to increase population health. Costs refer to the value of the resources involved in providing a health care intervention and managing side-effects, symptoms and disease related events; it includes for example, capital equipment, clinical and non-clinical staff, consumables, such as drugs and medical devices. It can also include other resources, outside the health services, such as the time of patients.

Outcomes are the effects of the intervention; it includes for example, broad outcomes such as life years gained, or more specific outcomes related to the interventions being evaluated.

As it is clear, economic evaluation is a comparative methodology, interested in incremental costs and outcomes.

There are 4 major models for economic evaluation in health care (Briggs et al., 2006). In the simplest model, cost-consequence analysis (CCA), the diverse costs and outcomes of the alternative technologies are calculated and reported in a disaggregated manner. The decision makers then interpret, synthesize or weight the diverse results as appropriate.

The second form of economic evaluation is cost-minimization analysis (CMA). In this case, it is we assumed explicitly that health outcomes (including both efficacy and safety/tolerability) are identical to all interventions under consideration; costs are then compared, and the least costly intervention will be preferred. This methodology is seldom appropriate as it is highly unlikely that two interventions are in reality identical. Moreover, a lack of statistical significance in a study powered to detect differences between interventions is not enough to conclude that two interventions are identical.

In cost-effectiveness analysis (CEA) we measure the outcomes in natural units (e.g., the primary outcome measure of the intervention) and calculate the ICER (e.g., additional cost unit of health outcome). The ICER is the ratio of the difference on health costs to the difference in health outcomes.

The ICER by itself does not indicate the optimal technology; it simply indicates how much expensive is an health improvement using a technology, compared with other technology, in monetary terms (value for the money). An ICER is a positive fact about two alternatives, not a normative argument about which treatment is better. One sub-type of CEA is cost-utility analysis (CUA) which all outcomes are expressed into a single metric (quality-adjusted life years, or QALYs) which permits comparisons across several interventions from diverse areas. QALYs includes in a single metric the most important features of a health intervention: survival in terms of life-years and quality of life. Because the valuations made in certain health states are related to the utility theory, this subset of CEA analysis can be referred to as cost-utility analysis.

Finally in cost-benefit analysis (CBA), monetary values are put into outcomes by assessing society's willingness to pay a certain benefit. The costs of interventions are compared with the monetary values of the benefits, and technologies are adopted if the benefits outweigh the costs. CBA allows comparisons not just within the health care budget, but also between different areas of public expenditures, such as defense, justice education (Gray et al., 2011)

We can trace economic evaluation in health care into 2 directions: operations research/management science and welfare economic theory. In the first direction, it is viewed as a problem of maximization under constrains. Cost-effectiveness analysis (CEA) is the model generally used to apply these principles of resource allocation, allowing production efficiency to be addressed, where a health outcome is being produced at the lowest possible cost.

The other direction relates to welfare economics, in which social welfare is the sum of total individual utilities, and resource allocation decisions should be directed towards the policies offering the largest positive social welfare improvements (Pearce & Nash, 1981). Cost-utility analysis is the model used, based on the concept of Pareto improvement, allowing allocative efficiency to be addressed.

In order to judge if an intervention is cost-effective in a CEA, we need to determine the maximum acceptable ICER (willingness-to-pay threshold (WTP)), which is how much the decision-maker is willing to pay for an additional health gain (Laupacis et al., 1992). There are four ways to determine this value: rule of thumb, a league table approach, a revealed and preference approach (Weinstein et al., 1996b). Surprisingly, the most common method used in several countries to define a maximum acceptable ICER is through more or less arbitrary rules of thumb, without transparent empirical analytical basis. In the UK, NICE sets out this value between £20,000-£30,000, while in Ireland (HIQA) it stipulates between €20,000-€30,000 (Rawlins, 1999). The World Health Organization uses a similar approach, suggesting as a rule of thumb that an intervention is cost-effective if less than three times the country's GDP (Tan-Torres Edejer, 2003).

Before developing a model, the problem to be addressed must be clearly defined, and the decision about the most appropriate model to use should be dependent on factors such as the interaction of patients, time horizon, number of health states (Cooper et al., 2007). The most common types of models used are: (1) decision tree models for short timeframes; (2) Markov models for recurrent events and (3) simulation models for a large number of health states. Another important point to decide is which perspectives to use: payer's perspective versus society's perspective, as the choice of perspective may result in different conclusions about the same interventions. The payer's perspective included only direct costs incurred by the payer, while the alternative perspective considers all

costs regardless of who incurs them (e.g., losses of productivity, informal care costs from family and friends). The NICE recommends that the cost perspective adopted for the reference case should be that of the payers perspective (NHS) and Personal Social Services (PSS), as this approach it is more consistent and objective (NICE, 2008). We need to adjust costs and benefits to allow adjust for time preference. Moreover we need to adjust costs to inflation and currency.

Discounting captures the idea that future costs are worth less than those occurring now, mainly because of time preference. We prefer to have resources now or receive benefits now, rather in the future. This reflects the human short-view of life. To account for time preference and opportunity cost, a discount rate is applied to costs and benefits. This discount rate includes uncertainty about the future and pure time preferences. The risk-adjusted time preference rate is estimated as 1.5% annually (Treasury, 2003). In the UK, as the expected inflation over time is estimated as 2% annually, the UK government guidance is that discount rate should be 3.5% for the first 30 years and 3% thereafter (Gray et al., 2011). Typically CE studies assume a time-discount rate of between 3% and 5%, being 3% the most common discount rate (Glick et al., 2014; Weinstein et al., 1996a)

Chapter 2 - Methods

2.1 Model design

A Markov model analyses uncertain events over time and is therefore appropriate where the strategies being evaluated are of a sequential or repetitive nature, such as a CCR screening program, where costs and effects spread over a long period of time. In a Markov model a patient is in one of a finite number of mutually exclusive health states, and the model is run for several cycles of equal length in which there are transitions between health states. The movements between states are defined by transition probabilities and rewards, such as costs and benefits, are earned at the end of each cycle. Although transition probabilities are constant over time (Markovian assumption), it is possible to incorporate some aspects of memory using tunnel states and time dependencies.

2.1.1 Model Structure overview

A Markov model was developed to simulate the natural history of colorectal cancer and to estimate the cost-effectiveness of five strategies for CRC screening in Portugal, as well as no screening, in 50-year-old individuals at average risk for colorectal cancer.

The CRC model includes a screening component and a natural history component. The screening component incorporates assumptions relevant to the screening programme, such as adherence, tests performance, screening intervals, type of tests used, while the natural history component incorporates assumptions about the progression from adenoma to CRC.

The Markov model contained 26 mutually exclusive and exhaustive health states and the five screening strategies were superimposed on the natural history of the model.

Screening began at age 50 years and stopped at age 75 years, and persons were followed until death or 100 years of age. If a screening test was positive, colonoscopy was offered, and biopsy or polypectomy were performed according to findings. All colonoscopies were performed with anaesthesia assistance.

The models run through a maximum of 50 cycles 1-year-cycles, and the rewards (costs and outcomes) are accrued within each cycle and accumulate throughout the life cycle of the model. At the end of each cycle, the members of the cohort return to the same health state and/or to other(s) health states, according with predetermined transition probabilities. Additional costs, outcomes and count progressions associated with relevant events occurring in the full set of pathways for each state during a cycle ('transition subtrees'), are also accrued.

The model uses a payer perspective (Portuguese NHS as the primary payer). All costs and outcomes were discounted at 3,0% to adjust for time preference. All money variables will be adjusted for 2020 inflation. Half-cycle correction was used, as it is assumed, that, on average, state transitions occur half-way through the cycle.

Though there is no official maximum acceptable ICER in Portugal for health technologies evaluations, we assumed a threshold of 30,000€ per QALY, as recommended by The National Institute for Health and Care Excellence (NICE, 2013). The simulation was performed using TreeAge Pro HealthCare 2021, R2 (TreeAge Software Inc., Williamstown, MA, USA).

2.1.2 Screening strategies

We modelled five screening strategies: (1) FIT every 2 years (FIT 2/2y strategy), which is the strategy chosen in Portugal by the NHS (Ministério da Saúde, 2017); 2) colonoscopy with anaesthesia assistance every 10 years (colonoscopy 10/10y strategy); 3) colonoscopy with anaesthesia assistance, with the second screening colonoscopy at a 3-year interval and thereafter every 10 years (colonoscopy 3/10y strategy); 4) CT-colonography every 5 years (CT 5/5y strategy); 5) FIT every year (FIT 1/1y strategy) (Table 1).

Under our model, all colonoscopies are performed with anaesthesia assisted sedation administered by an anaesthesiologist, as it is common practice in Portugal since 2014.

Table 1 - Screening strategies

Screening strategy	Screening test	Interval
FIT 2/2y	Fecal immunochemical test	2
Colonoscopy 10/10y	Colonoscopy assisted with anaesthesia	10
Colonoscopy 3/10y	Colonoscopy assisted with anaesthesia	(3), 10 [#]
CT 5/5y	CT-colonography	5
FIT 1/1y	Fecal immunochemical test	1

[#]First uptake after 3 years of the initial colonoscopy, and then at 10-year intervals

2.1.3 Model population

An arbitrary cohort of average-risk persons for CRC at the age of 50 entered the model and were distributed, before the process begins, into one of the following 7 health states (according to the prevalence of adenomas and CRC in the population): (1) normal mucosa, (2) low-risk adenomas, (3) advanced adenomas (defined as either ≥ 1 cm, villous histology or high-grade dysplasia), (4) preclinical CRC stage I, (5) preclinical CRC stage II, (6) preclinical CRC stage III and (7) preclinical stage CRC IV (Sharma, 2020). The cohort population

transitioned between 26 health states, in annual cycles, based on transition probabilities estimated from the literature. The model run until death (there are three absorbing states) or by 50 cycles (Table 2).

Table 2 - Initial distribution of patients across health states

Health state	Base case (range)	SD	Source
No polyp	0.680	0.02	(Sharma, 2020)
Non-advanced adenoma	0.251 (0.05-0.30)	0.03	(Sharma, 2020)
Advanced adenoma	0.063 (0.015-0.09)	0.02	(Sharma, 2020)
Preclinical CRC	0.0060	-	(Krilaviciute et al., 2017)
Stage 1	0.0035	0.003	(Sharma, 2020)
Stage 2	0.0013	0.0003	(Sharma, 2020)
Stage 3	0.0010	0.0003	(Sharma, 2020)
Stage 4	0.0002	0.0003	(Sharma, 2020)

2.1.4 Health States

The model aims to replicate the natural history of CRC and CCR screening using the following health states: (1) Normal mucosa; (2) Low-risk adenomas; (3) Advanced adenomas (defined as either ≥ 1 cms, villous histology or high-grade dysplasia); (4) Preclinical CRC stage I; (5) Preclinical CRC stage II; (6) Preclinical CRC stage III; (7) Preclinical stage CRC IV; (8) Symptomatic CRC stage I; (9) Symptomatic CRC stage II; (10) Symptomatic CRC stage III; (12) Symptomatic CRC stage IV; (13) Treatment/Surveillance CRC stage I; (13) Treatment/Surveillance CRC stage II; (14) Treatment/Surveillance CRC stage III; (15) Treatment/Surveillance CRC stage IV; (16) Natural history low-risk adenomas; (17) Natural history advanced adenoma; (18) Natural history preclinical CRC stage I; (19) Natural history CRC stage II; (20) Natural history CRC stage III; (21) Natural history CRC stage IV; (22) Surveillance after low-risk adenoma polypectomy; (23) Surveillance after advanced adenoma polypectomy;

(24) Death from background mortality; (25) Death from CRC and (26) Death from colonoscopy.

2.1.5 Transition Probabilities

The probabilities of transition between health states, the compliance rate, the age- and stage specific incidence and mortality rates of CRC, and other input parameters will be extracted after a systematic literature review (Table 7 – Annual transition probabilities (attachments)). The probability of background death was age dependent and data was extracted from Statistics Portugal (Instituto Nacional de Estatística, 2021). The probabilities of CRC-related death were stage specific, and it was assumed that after six years of survival the probability of death was fixed (Table 8 - Probability of death (attachments))

2.1.6 Test performance and compliance

The performance and the compliance with the screening tests were extracted after a systematic literature review (Table 9 - Screening test performance (attachments)). In the base case, the adherence for initial screening varied according to the test (Table 3).

Table 3 - Adherence to screening (real-world)

Variable	Base case (range)	SD	Source
Adherence with initial screening:			
Fecal immunochemical test	0.42 (0.34-0.51)	0.08	(Telford et al., 2010)
Colonoscopy	0.60 (0.3-0.7)	0.1	(Frazier et al., 2000; Telford et al., 2010)
CT-Colonography	0.22 (0.15-0.32)	0.22	

Probability of undergoing each screening round after initial screening	0.73 (0.5-0.9)	0.03	(Telford et al., 2010)
Follow-up colonoscopy for a positive screening test	0.80 (0.50-0.90)	0.02	(Frazier et al., 2000; Wong et al., 2015)
Never adherent to a screening test	0.20 (0.10-0.50)	0.2	Assumption
Follow-up colonoscopy after polyp removal	0.80 (0.60-0.90)	0.2	(Frazier et al., 2000; Wong et al., 2015)

For colonoscopy assisted with anaesthesia, as there are no empirical data with which to estimate the initial adherence in an organized screening program, we assumed an initial adherence of 60%. At each screening interval (after the initial screening) we assumed that a random 73% of the cohort underwent screening, independent of whether they were compliant with past tests. We assumed that 20% of the persons were never adherent to screening (drop out). This sub-cohort of patients moved to the natural history health states of the model immediately after the first screening round. For the follow-up colonoscopy after a positive screening test, we assumed a compliance rate of 80%. The same compliance rate was assumed for the surveillance colonoscopy after polyp removal or CRC diagnosis. Among patients who had symptomatic presentation of CRC, it was assumed that all patients undergo colonoscopy with biopsy.

2.1.7 Costs inputs

The costs were calculated after measuring the quantities of resources used, using the appropriate physical units (Table 4). Only direct medical costs are included. Costs were derived from two national reference costs datasets and the contractual framework for hospital care produced by the Portuguese Ministry of Health (ACSS, 2021a, 2021b, 2021c).

Costs for the initial two years of CRC treatment (stages II to stage IV) use the amount that hospitals receive under the prospective payment pilot program for CCR treatment. For stage I CRC, we assumed a different reimbursement, as no treatment, other than surgery is performed (e.g., chemotherapy or radiotherapy). In stage 1, hospitals are reimbursed in the first year, for the surgery performed, according to the cost of the appropriate Portuguese classification for Diagnosis-Related Group (DRG) (code 221, 'procedimentos major do intestino grosso', severity 2) plus the price of the consultations and tests required for surveillance. The cost of a patient with a death related with CRC was assumed to be reimbursed under DRG code 240, severity 4.

We assumed that no co-payments were performed by patients, since in Portugal, all consultations and tests requested by primary care physicians are free of charge for patients in point-of-care.

Table 4 - Medical Costs (2020 euros)

Variable	Cost (€)	Source
Screening		
Primary care Physician Visit	15	(ACSS, 2021c)
Fecal immunochemical test	3	(ACSS, 2021b)
Screening colonoscopy	397	(ACSS, 2021a)
CT colonography	160.60	(ACSS, 2021a)
Laboratory tests for colonoscopy	17.81	(ACSS, 2021b)
ECG	3.87	(ACSS, 2021b)
Colonoscopy assisted with anesthesia	169.73	(ACSS, 2021b)
Histopathological examination	12.75	(ACSS, 2021b)
Hospital care		
Colonoscopy perforation	4,340.10	(ACSS, 2021a)
Gastroenterology/ consultation*	Oncology 75	(ACSS, 2021c)
Abdominal CT	84.50	(ACSS, 2021a)
Pelvic CT	61.59	(ACSS, 2021a)

Carcinoembryonic antigen	7.20	(ACSS, 2021a)
Laboratory tests for colonoscopy	16.6	(ACSS, 2021a)
ECG	6.50	(ACSS, 2021a)
Colonoscopy assisted with anesthesia	179.1	(ACSS, 2021a)
Polypectomy	64.50	(ACSS, 2021a)
Cost of colorectal cancer		
Stage I:		
Year 1	4,340.10	(ACSS, 2021a)
Year 2	620.98	(ACSS, 2021a)
Stage II-IV:		
Year 1	11,867.0	(ACSS, 2021c)
Year 2	5,245.0	(ACSS, 2021c)
Stage I-IV:		
Year 3	302.9	(ACSS, 2021a)
Year 4	228.29	(ACSS, 2021a)
Year 5	302.09	(ACSS, 2021a)

2.1.8 Utility inputs

We assigned utilities to the health states used in the model, to calculate quality adjusted life-years (QALYs). We assigned a utility of 1 to patients without a diagnosis of cancer (Table 5).

Table 5 - Utilities

	Base case (range)	SD	Source
No cancer	1 (0.91-1.0)	0	(Telford et al., 2010)
CRC			
Stage I	0.74 (0.70-0.78)	0.22	(Ness et al., 1999)
Stage II	0.67 (0.64-0.70)	0.21	(Ness et al., 1999)
Stage III	0.55 (0.50-0.60)	0.19	(Ness et al., 1999)
Stage IV	0.25 (0.24-0.26)	0.075	(Ness et al., 1999)

Death	0.00	0	(Telford et al., 2010)
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2.1.9 Modelled scenarios

Two scenarios were considered to evaluate the impact of adherence on screening: (i) Scenario 1 – Real World Scenario: where real-world adherence rates are assumed for all screening tests (initial and uptake) and follow-up colonoscopies; (ii) Scenario 2 – Perfect Adherence Scenario: where 100% adherence rates are assumed for all screening tests (initial and uptake) and follow-up colonoscopies (Table 6.).

Table 6 - Scenarios

Scenario	Adherence at initial screening test	Adherence after initial screening test	Colonoscopy for a positive screening test
Scenario 1	Base case estimate	Base case estimate	Base Case estimate
Scenario 2	100%	100%	100%

2.2 Analysis

2.2.1 Outcomes

The primary outcome was the incremental cost-effectiveness ratio between the different screening strategies. The numerators were the differences in costs for each strategy in relation to the previous strategy (ranked in order of costs), and the denominators were the differences in QALYs gained.

CE ranking tables will be presented , as well as CE planes. In this diagrams differences in effect between alternative screening strategies are plotted along the horizontal axis, and the difference in cost on the vertical axis.

In addition, clinical outcomes were presented as totals over 1000 patients over the model lifetime. The following clinical outcomes were reported: QALY gained, LYG, number of CRC cases, number of CRC deaths, CRC incidence reduction, CRC mortality reduction, number of screening tests, number of colonoscopies for follow-up/ surveillance and costs of screening strategy. The outcomes will be presented for the two modelled scenarios.

2.2.2 Sensitivity analysis

Uncertainty was estimated using deterministic and probabilistic sensitivity analysis (PSA) to assess the robustness of the conclusions to changes in critical input parameters in the base case scenario (scenario 1). For the deterministic sensitivity analysis, a Tornado diagram was used to evaluate the individual input parameters (using the intervals defined in the input tables)with largest impact in the model output (results presented as incremental net monetary benefits) between the pair of strategies: Colo 3/10y vs FIT 1/1y. The individual parameters were varied across a plausible range and threshold values (at which two strategies have equal expected values) were identified if occurred. For the PSA analysis, we performed a probabilistic Monte Carlo simulation recalculating the model with 10,000 trials in which multiple parameters sampled from appropriate distributions (representing uncertainty around the base case estimate; using the base case as the mean and standard deviations (SD) described in tables) are varied simultaneously, with the resulting cost and effect pairs being recorded. Results will be presented using acceptability curves, acceptability at WTP. An ICER scatterplot between the most CE strategy and FIT2/2y will be presented.

Chapter 3 – Results

The perfect adherence scenario, compared to the real-world scenario (base case), will give information to the decision makers, about the impact of adherence on the outcomes of the model. In case the best strategy in this scenario of perfect adherence differs from the baseline scenario, it may be a strong argument for the decision-makers to support policies to increase patient adherence to this strategy.

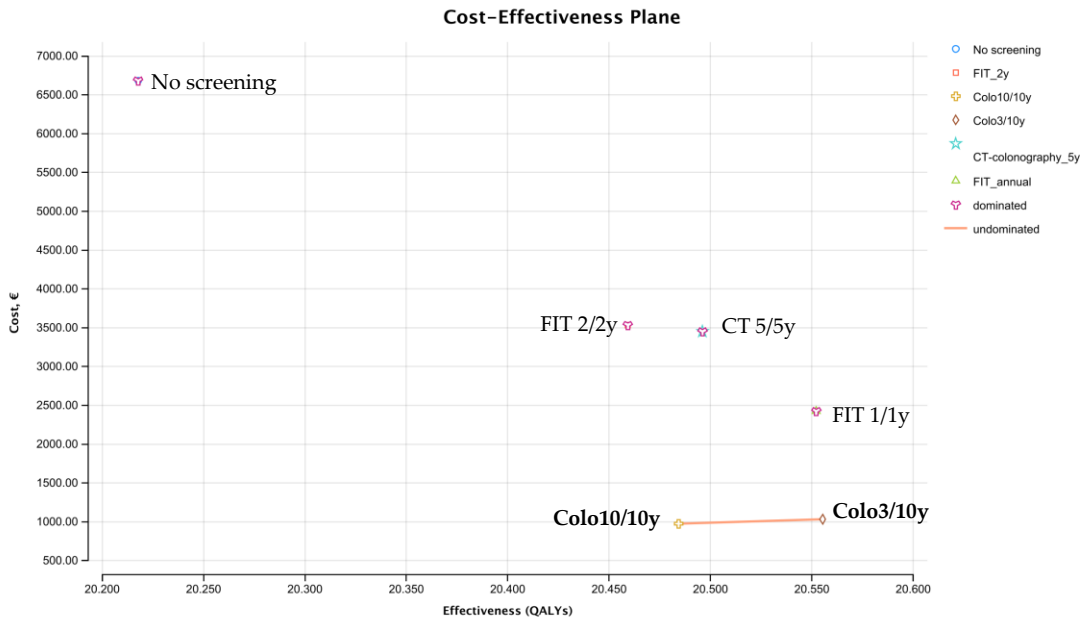
3.1 Scenario 1 – Real world scenario

In the real world scenario, assuming base case estimates for screening adherence and follow-up colonoscopies (when indicated), the most expensive strategy was no screening costing 6,683€ per person. The cheapest strategy was colonoscopy 10/10y which costs 974.25€ per person. The most effective strategy was colonoscopy 3/10y providing 20.555 QALYs and the least effective strategy, was no screening providing 20.218 QALYs .

When comparing screening strategies incrementally, we must calculate the ICER (primary result) against the next most expensive strategy that is not dominated; we observe that colonoscopy 3/10y is the most cost-effective strategy with an ICER of 802.07€ per QALY (clearly below the WTP of 30 000€/ QALY), compared with colonoscopy 10/10y. In Table 10 - Cost-effectiveness Report –

Real-World Scenario(attachment), a CE ranking table of the real world scenario, shows the different screening strategies ranked in ascending order of cost

Figure 1- Cost-effectiveness plane - Real World Scenario



All other strategies (all stool-based and CT screening strategies) are absolutely dominated by the colonoscopy screening strategies. FIT 1/1y, the strategy immediately above colonoscopy 3/10y in the CE ranking table, is absolutely dominated by colonoscopy 3/10y, as it is more costly (incremental cost of € 1,395.28€) and less effective (incremental effectiveness of -0.003 QALYs). Although the difference in effectiveness is small (although significant because you are reporting differences in a single patient), the difference in costs is large, which has a large impact on the calculation on the cost-effectiveness results. In the cost-effectiveness plane we observe the cost-effectiveness frontier displayed as a line that connects colonoscopy 10/10y and colonoscopy 3/10y (Figure 1). All the screening strategies that lie north and west (i.e., above and to the left) of this line are dominated by the strategies at the CE frontier. FIT 2/2 y, the CCR

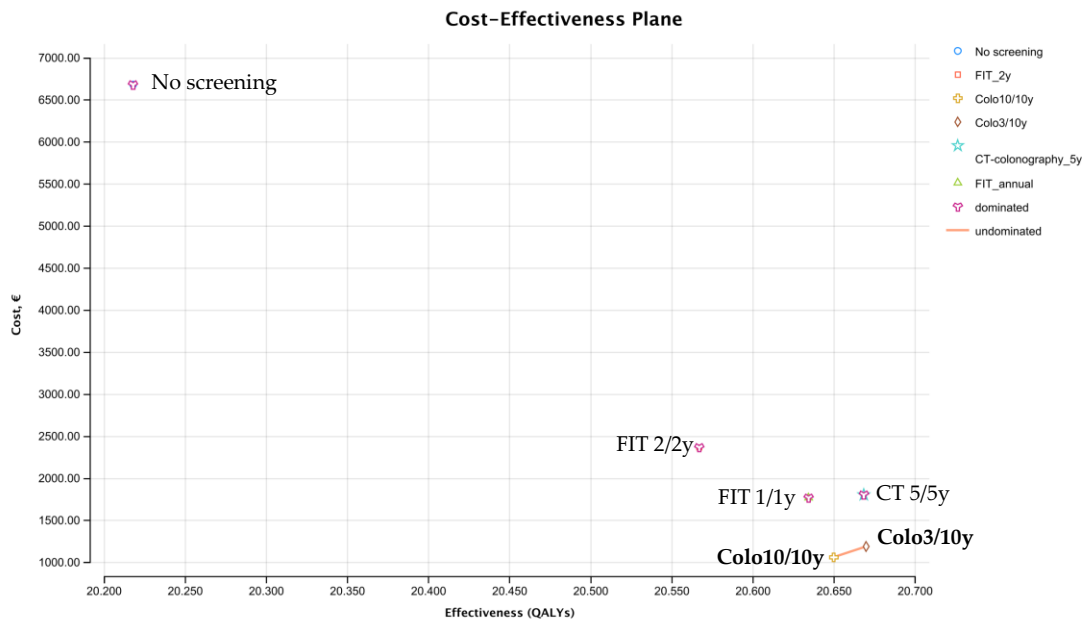
screening strategy used in Portugal, is the second with highest cost (3,533.33€), and the second least effective with 20.459 QALYs only surpassed by no screening.

The total number of LYG gained per 1000 persons was highest for FIT 1/1y (661.3 days) (Table 12 - Clinical outcomes per 1000 patients – Real-World Scenario(attachment)). Colonoscopy 3/10y resulted in the highest CRC incidence reduction (-64%). As expected, the total number of colonoscopies (screening and surveillance) were higher for colonoscopy 3/10 y strategy (n=4526). FIT 2/2 y showed the smallest gains in LYG (498.3 days) of all strategies, as well as the smallest reduction in the incidence of CRC (-37%) and the smallest reduction in mortality (-57%).

3.2 Scenario 2- Perfect adherence scenario

In the perfect adherence scenario, assuming 100% adherence for screening and follow-up colonoscopies (when indicated), colonoscopy 3/10y is the most cost-effective strategy with an ICER of 6,361.08€ per QALY (at WTP of 30 000€/QALY), compared with colonoscopy 10/10y (Table 11- Cost-effectiveness Report – Perfect Adherence Scenario(attachment)). All other strategies are absolutely dominated by the colonoscopy screening strategies (Figure 2).

Figure 2 - Cost-effectiveness plane - Perfect Adherence Scenario



FIT 1/1y, the strategy immediately below colonoscopy 3/10y in the CE ranking table, is absolutely dominated by colonoscopy 3/10y, as it is more expensive (incremental cost of € 580.04€) and less effective (incremental effectiveness of -0.035 QALYs). FIT 2/2 y, the strategy used in Portugal, is the second with highest cost (2,369.17€), and the second least effective with 20.567 QALYs only surpassed by no screening. The most expensive strategy was no screening costing 6,683.8€ per person. The cheapest strategy was colonoscopy 10/10y which costs € 1063 per person. The most effective strategy was colonoscopy providing 20.669 QALYs and the least effective strategy, was no screening providing 20.218 QALYs.

The total number of LYG gained per 1000 persons was highest for colonoscopy 3/10y (812.2 days) (Table 13 - Clinical outcomes per 1000 patients – Perfect Adherence Scenario(attachment)). Colonoscopy 3/10y resulted in the highest CRC incidence reduction (-80%) and greatest CRC mortality reduction (-91%). The total number of colonoscopies (screening and surveillance) were higher for colonoscopy 3/10 y strategy (6546). FIT 2/2 y showed the smallest gains in LYG (687.5 days) of all strategies, as well as the smallest reduction in the incidence of CRC (-55%) and the smallest reduction in mortality (-76%). The no screening

strategy had the highest cost (6,683,805.71€), with colonoscopy 10/10y being the least expensive (1,063,366.85€) , followed by colonoscopy 3/10y (1,190,483.53€).

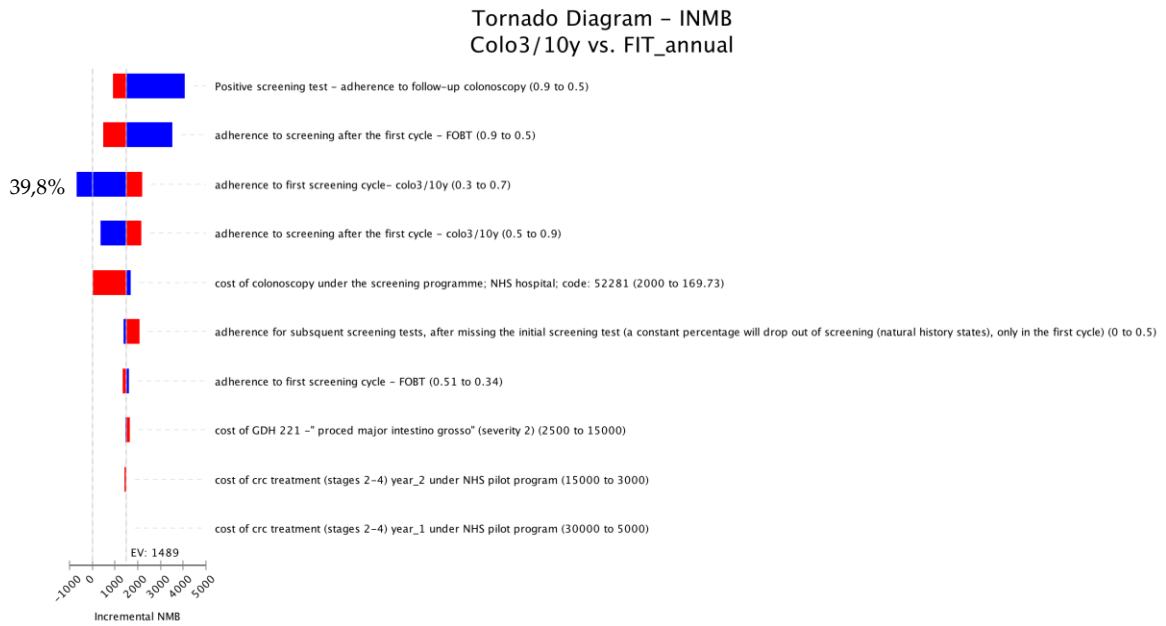
3.3 Sensitivity analysis

3.3.1 Univariate analysis

The impact of adherence and cost parameters on the cost-effectiveness of colonoscopy 3/10 strategy versus FIT 1/1y strategy were evaluated using a Tornado diagram using incremental net monetary benefits as the output (Figure 3). We evaluated adherence to first screening test, uptake tests, drop-out from screening and adherence to follow-up colonoscopy when FIT was positive. Cost of the CRC treatment and cost of the screening colonoscopy were also evaluated.

The only input that change the most cost-effective strategy, was adherence to baseline colonoscopy; when the rate of adherence is below 39,8%, FIT 1/1y becomes the most cost-effective strategy (the incremental NMB change from positive to negative). All other inputs (over the defined parameter's uncertainty range) do not alter colonoscopy 3/10y as the most cost-effective strategy. Interestingly, even with colonoscopy costing 2,000€ (the upper limit of the range used in this sensitivity analysis), colonoscopy 3/10y is still is the most cost-effective strategy.

Figure 3 – Tornado diagram: colonoscopy 3/10y versus FIT 1/1y



3.3.2 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis, colonoscopy 3/10 screening strategy was cost-effective over all other strategies in 84.77% of the simulations at a WTP of €30,000/QALY (Figure 4). FIT 1/1y screening strategy was only cost-effective in 15.23% of the simulations. To evaluate the percentage of iterations WTP that favour each screening strategy over a range WTP, an acceptability curve was produced (Figure 5). Again, in an WTP range (€0 – 60,000€) , colonoscopy 3/10y is the more cost-effective strategy. FIT 2/2 y, was never a cost-effective strategy, in the 10,000 iterations.

Figure 4 - Monte Carlo acceptability at WTP

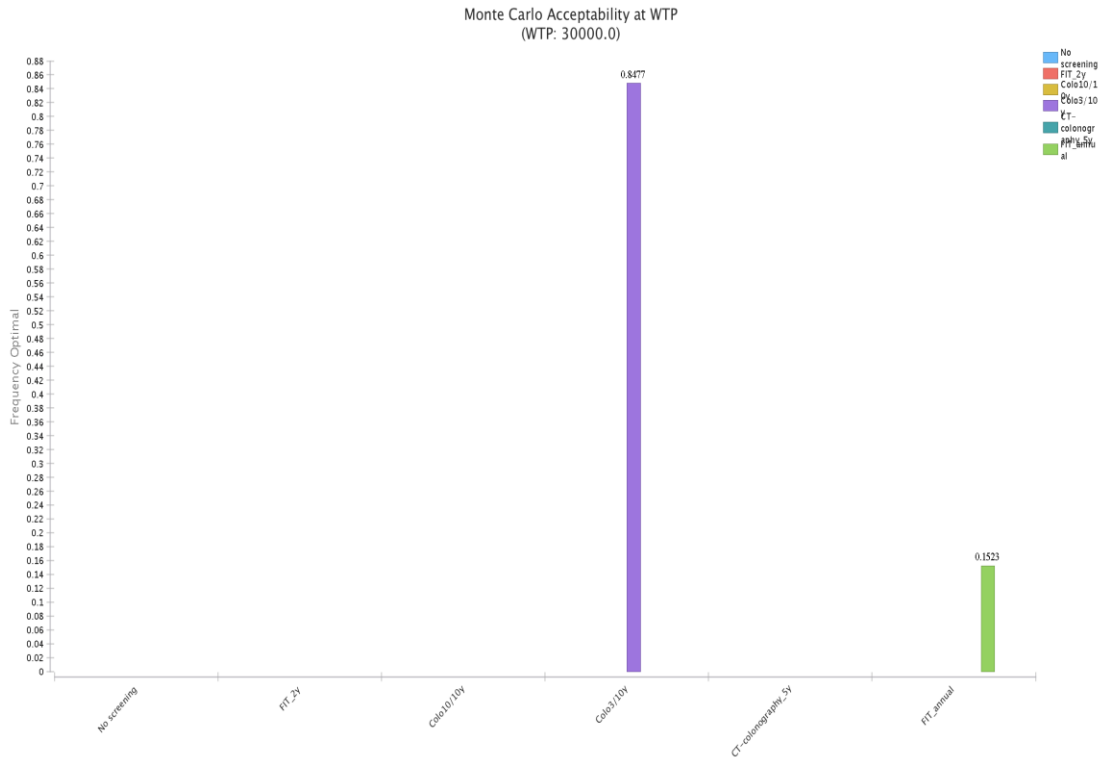


Figure 5 - CE acceptability curve

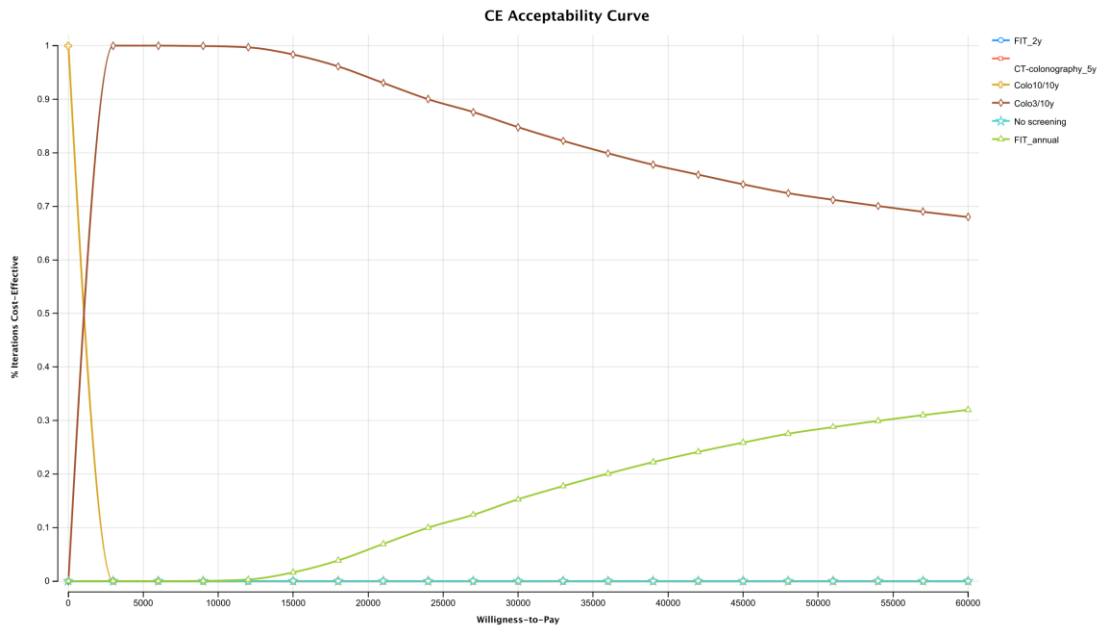
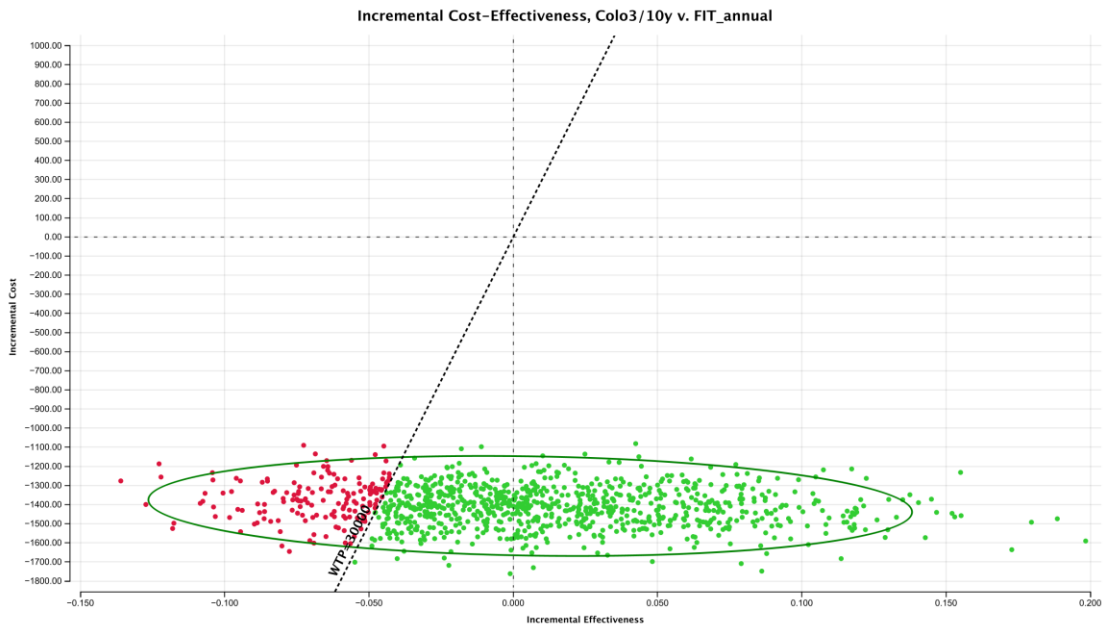


Figure 6 - ICE scatterplot: Colonoscopy3/10y versus FIT1/1y



Chapter 4 - Discussion

In the Portuguese context, the most cost-effective strategy for colorectal cancer screening is colonoscopy every 10 years, with the first follow-up colonoscopy performed 3 years after completion of the baseline colonoscopy. The colonoscopy based-strategies (colonoscopy 3/10y and colonoscopy 10/10y) absolutely dominate all stool-based strategies as well as CT-colonography, with ICERs clearly below the WTP threshold of 30,000€ per QALY and the largest net monetary benefits (NMB). Choosing a different strategy resulted in lower effectiveness and higher costs, making such an option not rational and undesirable. The biennial FIT strategy, although positive in reducing CCR incidence and mortality compared with no screening, is the least cost-effective choice among the 5 strategies modelled.

Our findings, in which colonoscopy-based strategies are most cost-effective, are consistent with other models reported in the literature, although there are studies with different results (Zhong et al., 2020). Telford et al, used a Markov probabilistic model to estimate the most cost-effective strategy for CCR screening in Canada; colonoscopy every 10 years was the most cost-effective strategy with an ICER of 6,133€ per QALY when compared to FIT performed annually (Telford et al., 2010). In a study by Barzi et al evaluating 13 screening strategies, including FIT, colonoscopy was the most effective strategy with the highest effectiveness, but also the lowest total cost per patient(\$2861) (Barzi et al., 2017). They showed

that annual FIT was dominated by colonoscopy every 10 years. In our study, we found similar results, as annual FIT is absolutely dominated by colonoscopy, with an ICER of – 44,461.97€ per QALY (FIT 1/1y versus colonoscopy 3/10y). The absolute dominance of colonoscopy over all other strategies, observed in our model, are probably explained by two main factors acting simultaneously in the Portuguese context: (1) relatively low cost of anaesthetic-assisted colonoscopy (compared to other developed countries), and the high reimbursement received by NHS hospitals during the first two years of CCR treatment.

In our model colonoscopy 3/10y is more cost-effective than colonoscopy 10/10y, with an ICER of 802.7€ per QALY, in the base case scenario. Colonoscopy every 10 years is the strategy generally evaluated in CCR models. As far as we know, this is the first time, a colonoscopy 3/10 y strategy has been included in a model, aiming to decrease the number of missing lesions in the baseline colonoscopy (Wolf et al., 2018).

Our results are reinforced by the perfect adherence scenario, as there are no changes in the main conclusions. Colonoscopy-based strategies continue to dominate all other strategies and the cost-effectiveness ranking remains unchanged. These results are further supported by the 10,000 iterations performed in a Monte Carlo simulation, in which colonoscopy 3/10y is the most cost-effective strategy in more than 80% of the iterations. The only situation in which FIT is more cost-effective than colonoscopy is for initial adherence for colonoscopy below 39.8% *ceteris paribus*, reinforcing the importance of health policies to increase adherence.

In our model, the assumption of adherence for initial screening with colonoscopy based strategies was 60%. Individual adherence can be influenced by many factors, such as, education about screening, test characteristics and physician recommendation. Regarding colonoscopy adherence, two major factor influencing patient compliance is ensure that they will not have of pain and

safety. The colonoscopy adherence rate used in the cost-effectiveness models for base case estimates is variable, from 22% to 60% (Greuter et al., 2016; Sekiguchi et al., 2016; Zhong et al., 2020). In our study, we assumed the upper limit of this range, as colonoscopy was modelled under anaesthesia assistance (in Portugal, almost all colonoscopies requested by NHS primary care physicians are performed under anaesthesia in an open access basis, free of charge at the point of care), which will very plausibly increase the adherence rate. In 2015, a US survey found that 45.3% of adults aged 50 to 54 years reported screening with either colonoscopy or sigmoidoscopy (Wolf et al., 2018).

There is agreement between our model estimates and other studies about the clinical impact of different screening strategies on the natural history of CCR. Screening colonoscopy 3/10y, the most cost-effective strategy in our model, prevented 64% of CRCs (129.7 CRC cases in the unscreened cohort) and gained 337.5 QALYs (per 1000 screened patients); improving screening for a perfect adherence scenario would prevent 80% of the CRCs cases and gain 451.9 QALYs. In a study by Ladabaum et al, the number of cases of CRC per 1000 persons was 105 in the unscreened cohort; colonoscopy every 10 years, averted 60 cases of CRC (57.2% reduction) using 4,404 colonoscopies (Ladabaum et al., 2019b). In our study, colonoscopy every 10 years used 3178 colonoscopies, whereas colonoscopy 3/10 y used 4526 colonoscopies. Again as expected, the least effective strategy, biennial FIT avoided only 55% of CCRs, and gained only 77.2% of the QALYs obtained by the colonoscopy 3/10y strategy, being more than six times more expensive compared to colonoscopy 3/10y.

Our model is the first cost-effective analysis performed in the Portuguese context, using the NHS perspective, using a Markov model replicating the natural history of colon cancer, as well as its current treatment according to CCR staging, where the five strategies were superimposed. In 2018, Areia et al published a study in which a cost-effectiveness analysis was performed between

2 strategies in the Portuguese context: biennial FIT and colonoscopy every 10 years (using no screening as baseline) (Areia et al., 2019). They concluded that biennial FIT was the most cost-effective strategy, as colonoscopy presented an ICER (103,633€ per QALY) above the WTP threshold. In reality, they were reporting the average cost effectiveness ratio (ACER), and not the ICER as it should have been done; the ICER between the two strategies is even much higher much (549,433€ per QALY). They used a societal perspective, which despite strong economic theoretical arguments for its use, is not the perspective used and recommended by most government agencies, such as NICE or the Infarmed - National Authority of Medicines and Health Products, due to its lack of consistency and objectivity, as it introduces a large number of discretionary costs (Briggs et al., 2006; Gray et al., 2011; NICE, 2008). In their model they only include 2 strategies, as they argue that including more strategies in the model would compromise the evaluation of the 2 strategies. This argument has no practical or theoretical support, as the quality of the model analysis is not dependent on the number of strategies included, as each strategy is an independent node in a Markov model. In our opinion, FIT 1/1 y should have been included, not least because FIT 2/2y is not endorsed from the major medical organizations (Bibbins-Domingo et al., 2016). The model structure blueprint raises some concerns, as we observe four absorbing states, which aren't death states, in which patients will be trapped inside that loop during the duration of the model, once moving to these states (surveillance stage 1 to 4). They used a colonoscopy compliance rate of 38%(we assume the same at all screening intervals). This assumption does not seem reasonable in the context of Portugal, since in Portugal colonoscopy is performed under anesthesia, free of charge when requested by primary care physicians of the NHS. The 38% adhesion rate used in the base case estimate was also used as the upper limit in the model's sensitivity analysis; it does not seem plausible that the baseline value is, at the same time, the upper limit in a

sensitivity analysis. Furthermore, using the initial adherence rate value of 38%, as the adherence rate for subsequent colonoscopies is surprising. In most studies, the rate of adhesion used for subsequent colonoscopies is higher between 60%-80% (Zhong et al., 2020).

The cost per patient of the 2 modelled strategies is very low: 11.9€ in the FIT strategy, 199.4€ in the colonoscopy strategy and 7.9€ in unscreened patient. This is difficult to understand as the cost of the cancer treatment, is the main driver of the total costs in any CCR screening program, give the price of new drugs and treatments. They should have used, as we did in our model, for objectivity and simplicity, the fixed reimbursement for the first 2 years of CCR treatment that it is being progressively implemented in Portugal. In their work, the cost of CCR per stage is not explicitly reported, as only cost data is showed in a supplementary table, with unit cost for several tests and procedures.

The limitations of our study include the fact that it remains a modelling exercise, using multiple health states, patients pathways, inputs and assumptions, and collecting data from multiple sources. The costs are derived from the Portuguese health care system, so care must be exercised when applying these results to other countries.

Chapter 5 - Conclusions

In conclusion, colonoscopy 3/10 years is the most cost-effective strategy for colorectal screening in Portugal. The stool based strategies and CT colonography strategies are more expensive and less effective than colonoscopy based strategies for CCR screening. The findings from this study should provide useful references for policy-makers to make budgetary planning and consolidate programme implementation at a population level.

According to our results, biennial FIT, the screening strategy used in Portugal, should be abandoned as it is the most expensive and less effective strategy for the NHS, and replaced by one of the two colonoscopy strategies.

The implementation of an organized screening strategy should include a cost-effectiveness analysis for the governments to take more rational decisions and better allocate resources in healthcare.

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Attachments

Table 7 –Annual transition probabilities(attachments)

Annual transition probabilities	Base case (range)	SD	Source
Probability of progression			
Low-risk polyp from normal	0.012	0.001	(Lee et al., 2010)
Advanced adenoma from low-risk polyp	0.024 (0.01-0.04)	0.001	(Lee et al., 2010)
CRC stage 1 from advanced adenoma	0.034 (0.02-0.10)	0.001	(Lee et al., 2010)
CRC stage 2 from CRC stage 1	0.583 (0.10-0.60)	0.02	(Lee et al., 2010)
CRC stage 3 from CRC stage 2	0.656 (0.15-0.70)	0.02	(Lee et al., 2010)
CRC stage 4 from CRC stage 3	0.865 (0.32-0.90)	0.02	(Lee et al., 2010)
Probability of symptomatic presentation			
CRC stage 1	0.065 (0.05-0.08)	0.01	(Lee et al., 2010)
CRC stage 2	0.26 (0.15-0.35)	0.02	(Lee et al., 2010)
CRC stage 3	0.46 (0.45-0.65)	0.02	(Lee et al., 2010)
CRC stage 4	0.92 (0.9-1)	0.02	(Lee et al., 2010)
Probability of developing adenomas following polypectomy			
Low-risk adenoma after polypectomy	0.07	0.01	(Lee et al., 2010)
High-risk adenoma after polypectomy	0.176	0.02	(Lee et al., 2010)

Table 8 - Probability of death(attachments)

	Base case	Source
Death from background mortality	Age-dependent	(Instituto Nacional de Estadística, 2021)
Death from colonoscopy	0.0002	(Leshno et al., 2003)
Death from CRC:		(NCRAS - National Cancer Registration and Analyses Service, n.d.)
Stage I		
5-year survival	0.932	
After 5 years	0.015	
Stage II		
5-year survival	0.770	
After 5 years	0.015	
Stage III		
5-year survival	0.477	
After 5 years	0.015	
Stage IV		
5-year survival	0.066	
After 5 years	0.03	

Table 9 - Screening test performance(attachments)

Variable	Base case (range)	SD	Source
Fecal immunochemical test			
Sensitivity to detect CCR	0.73 (0.603-0.839)	0.035	(Imperiale et al., 2014)
Sensitivity to detect advanced adenoma	0.238 (0.208-0.270)	0.02	(Imperiale et al., 2014)
Sensitivity to detect low-risk adenoma	0.0607-0.086)	0.01	(Imperiale et al., 2014)
Specificity	0.964 (0.958-0.969)	0.01	(Imperiale et al., 2014)
Colonoscopy assisted with anaesthesia			
Sensitivity to detect CCR	0.95 (0.900-0.970)	0.02	(Ladabaum et al., 2019a)
Sensitivity to detect advanced adenoma	0.90 (0.900-0.970)	0.015	(Ladabaum et al., 2019a)
Sensitivity to detect low-risk adenoma	0.85 (0.850-0.950)	0.015	(Ladabaum et al., 2019a)
Specificity	1		(Ladabaum et al., 2019a)
CT-Colonography			
Sensitivity to detect CCR	0.84 (0.756-0.924)	0.03	(Knudsen et al., 2016)
Sensitivity to detect advanced adenoma	0.84 (0.756-0.924)	0.03	(Knudsen et al., 2016)
Sensitivity to detect low-risk adenoma	0.57 (0.489-0.716)	0.03	(Knudsen et al., 2016)
Specificity	0.88 (0.777-0.883)	0.02	(Martín-López et al., 2014)

Table 10 - Cost-effectiveness Report – Real-World Scenario(attachment)

Dominance	Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB
undominated	Colo 10/10y	974.257		20.484			613,555,843
undominated	Colo 3/10y	1,031.175	56.917	20.555	0.071	802.070	615,627,823
abs. dominated	FIT 1/1y	2,426.457	1395.282	20.552	-0.003	-44,4661.97	614,138,406
abs. dominated	CT 5/5y	3,450.668	2,419.493	20.496	-0.059	-40,856.599	611,431,756
abs. dominated	FIT 2/2y	3,533.336	2,502.161	20.459	-0.096	-26,039.029	610,242,881
abs. dominated	No screening	6,683.806	5,652.631	20.218	-0.338	-16,748.074	599,849,913

Abbreviations: Incr, incremental; Eff, effectiveness; NMB, net monetary benefit

Table 11- Cost-effectiveness Report – Perfect Adherence Scenario(attachment)

Dominance	Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB
undominated	Colonoscopy 3/10y	1,063.367		20.650			618,428.59
undominated	Colonoscopy 3/10y	1,190.484	127.117	20.670	0.020	6,361.083	618,900.98
abs. dominated	FIT 1/1y	1,770.529	580.046	20.634	-0.035	-16,352.342	617,256.78
abs. dominated	CT 5/5y	1,807.395	616.911	20.668	-0.001	-43,9572.265	618,241.96
abs. dominated	FIT 2/2y	2,369.174	1,178.690	20.567	-0.103	-11,456.238	614,635.70
abs. dominated	No screening	6,683.806	5,493.322	20.218	-0.452	-12,155.390	599,849.91

Table 12 - Clinical outcomes per 1000 patients – Real-World Scenario(attachment)

Strategy	QALY Gained	LY Gained	CRC Cases	CRC Deaths	CRC Death Reduction	CRC cases Reduction	Tests	Colon	Total cost
Colonoscopy 10/10y	266.5	506.2	59.6	24.9	-60%	-54%	1,400	1,778	€ 974,257.41
Colonoscopy 3/10y	337.5	628.5	46.2	17.0	-73%	-64%	2,023	2,503	€ 1,031,174.86
FIT 1/1y	334.4	661.3	58.7	15.4	-75%	-55%	13,607	1,301	€ 2,426,457.19
CT 5/5y	278.3	537.5	62.3	20.7	-67%	-52%	2,568	990	€ 3,450,667.62
FIT 2/2y	241.4	498.3	81.5	27.0	-57%	-37%	7,022	755	€ 3,533,335.85
No screening	0.0	0.0	129.7	62.2	0%	0%	0	70	€ 6,683,805.71

Table 13 - Clinical outcomes per 1000 patients – Perfect Adherence Scenario(attachment)

Strategy	QALY Gained	LY Gained	CRC Cases	CRC Deaths	CRC Death Reduction	CRC cases Reduction	Tests	Colon	Total cost
Colonoscopy 10/10y	431.9	781.0	30.5	7.4	-88%	-76%	2,325	2,855	€ 1,063,366,85
Colonoscopy 3/10y	451.9	812.2	26.4	5.5	-91%	-80%	2,980	3,566	€ 1,190,483,53
FIT 1/1y	416.5	785.7	37.9	7.4	-88%	-71%	20,436	2,237	€ 1,770,529,28
CT 5/5y	450.5	812.0	29.7	5.7	-91%	-77%	4,307	1,715	€ 1,807,394,81
FIT 2/2y	349.0	687.5	58.9	14.8	-76%	-55%	10,735	1,327	€ 2,369,173,86
No screening	0.0	0,0	129.7	62.2	0%	0%	0	70	€ 6,683,805,71