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# Cost-utility analysis of genetic polymorphism universal screening in colorectal cancer prevention by detection of high-risk individuals

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ABSTRACT

*Background:* In the past 15 years numerous studies have been published on the involvement of low-penetrance susceptibility genes on the risk for developing colorectal cancer (CRC).
*Aim:* To perform an economic analysis of blood genetic testing in CRC screening in a population-based nationwide setting using polymorphisms in prostaglandin $E_2$ pathway genes as proof of concept.
*Methods:* A cost-utility analysis was performed from a societal perspective in Portugal comparing two strategies: blood genetic testing by the age of 40 versus no genetic screening under different assumptions of the cost of genetic testing (€10 and €30) and expected risk (1.5 to 5-fold). The adopted threshold was set at €44,870 (USD 50,000). The primary outcome was the incremental cost-effectiveness ratio (ICER) for a base case scenario.
*Results:* Polymorphism genotyping provided cost-utility only under the assumption of a 5-fold increased risk in the general population, providing ICERs of €44,356 and €30,389 for €30 and €10 tests, respectively.
*Conclusion:* Blood genetic screening for colorectal cancer has cost-utility only under specific assumptions of increased CRC risk and conservative cost estimates. Future studies should focus on defining genetic profiles because single-gene approaches are very unlikely to be cost-effective considering their modest predictive value.
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## 1. Introduction

Colorectal cancer (CRC) is a worldwide problem due to its high incidence and increasing burden as a reflection of the population growth, aging and adoption of a cancer-associated "westernized" lifestyle [1]. Its mortality is now the second leading cause of cancer mortality in Europe and the first in Portugal, accounting for nearly 16% of all cancer-related deaths [2]. Although many European countries are already performing colorectal screening, mainly by faecal occult blood testing (FOBT) or colonoscopy, many patients still present in advanced stages of the disease. One reason for this is the lower than desirable compliance rates that contrast with those reported for other recommended preventive strategies [3–6]. When cancer is diagnosed so late, patients are offered treatments like surgery, chemotherapy or radiotherapy that are expensive, impair their quality of life and still offer a poor prognosis [2]. This might be a reason not only to target screening but also to pursue alternative or additional screening strategies, such as blood testing for genetic changes that might be responsible for an increased risk for CRC [7,8].

In fact, it is expected that a large number of common low-penetrance genetic variants, each exhibiting a small influence on the risk, could be involved in the occurrence of colorectal tumours [9,10].

Our group has previously identified a panel of tag SNPs in cyclooxygenase-2/prostaglandin $E_2$ (COX-2/$PGE_2$) pathway genes as risk biomarkers for CRC development [7]. A large body of epidemiological and functional data has highlighted the central role of this pathway in colorectal carcinogenesis by triggering several

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oncogenic signalling pathways regarded as hallmarks of cancer, including inhibition of apoptosis, stimulation of cell proliferation and angiogenesis [11,12]. Overall, by 2010 over 600 studies had been published, reporting 445 polymorphisms in 110 different genes. However, no publication has yet addressed the suitability of genetic variants as a tool to improve current screening strategies from an economic perspective, by targeting a population to whom an earlier diagnostic colonoscopy could be recommended [8].

Therefore, with this study we set out to perform a cost utility analysis of the characterization of a population for common genetic variations in COX-2/$PGE_2$ pathway, as proof of concept, versus no genetic testing in CRC screening, trying to identify individuals that, until the results of the genetic test are known, are all presumed to be at average risk only.

## 2. Methods

### 2.1. Study population

Portuguese adults 40 years old were considered at risk for developing colorectal cancer in the future and were included in a cost utility analysis comparing blood genetic testing nationwide versus no genetic testing, which is the current practice.

A societal perspective was adopted by including the cost to the health system, patients, families and employers, thereby representing the public interest rather than that of any specific group, in accordance with the recommendations for reporting cost-effectiveness analyses [13–15].

### 2.2. Model structure

A cost utility model was chosen in order to compare the two strategies, blood genetic testing screening versus no screening. Different risks were assumed for the polymorphism and all available treatment effects possible, plus their transition probabilities, as shown in Fig. 1. Each branch corresponds to a clinical option for every state (circle) and on the far right are the terminal states (triangles) for each possibility, corresponding to the two final health states, dead or alive.

The time horizon of the study is from the age of 40 years to a diagnosis of cancer or death from another cause. The screening test is applied once only and negative tests are not repeated. For patients with a colorectal cancer diagnosis the time horizon of follow-up after a curative treatment is 5 years.

The currency used is the euro (€) and costs are given in 2018 prices. Prices from previous years were adjusted for inflation with a conversion tool available online from Pordata [16]. The discount rate was set at 3% for all cost and effectiveness data for the base case scenario, ranging in the sensitivity analysis between 0 and 5% in accordance with published guidelines [13–15,17]. The software used was TreeAge Pro 2009 (TreeAge Software, Williamstown, MA, USA).

For the reporting of this economic evaluation we adopted the suggestions of four guidelines, two for authors and peer reviewers of economic submissions and two for good practice in decision-analytic modelling in health technology assessment [18–25].

### 2.3. Clinical data

Data on clinical probabilities were obtained after an extensive review of the literature on systematic reviews or meta-analyses for the best available estimates for each transition probability in terms of adherence to screening, distribution by cancer stage, efficacy of treatments, all possible adverse events and stage disease-specific survival rates.

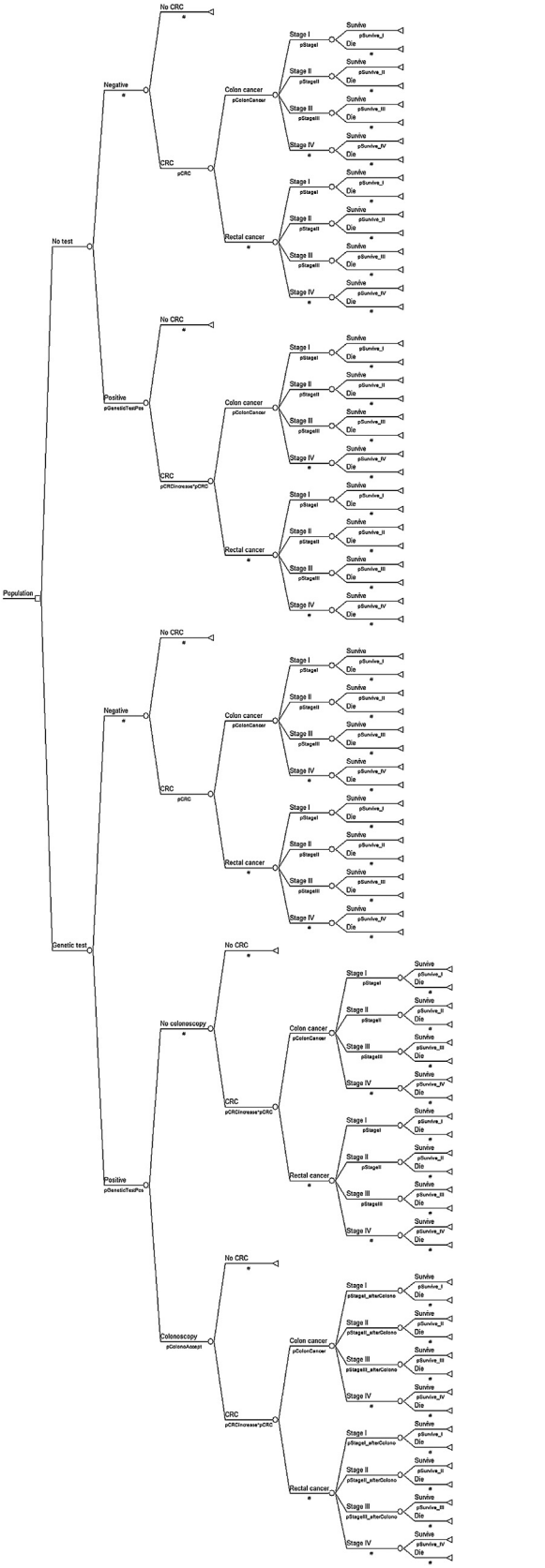


**Fig. 1.** Cost utility model representing the two main strategies: genetic colorectal screening versus no screening. The tree and its arms are intended to describe all possible clinical options for patients at risk for colorectal cancer (CRC) development. Each branch is followed by options (circle) that might exist in real life and on the far right are the terminal states (triangles) where patients at these stages can be accounted for by their survival or not, and respective quality of life in terms of utilities.

### 2.4. Cost data

Direct medical costs were estimated from national sources for surveillance costs (blood genetic testing and colonoscopy procedures after a positive genetic test, including the user fees if applicable, but without related administrative costs'), health state costs (depending on location of cancer in colon versus rectum, disease–stage and corresponding treatments) and adverse event costs (for both colonoscopy procedures and all possible colorectal cancer treatments available, that is, surgery, chemotherapy, radiotherapy and possible combinations). Direct non-medical costs were also taken into consideration for resources use, such as working days lost, frequency of visits to healthcare providers and transport. No assumptions were made for indirect costs such as time lost by relatives or caregivers, work loss, worker replacement or productivity changes.

Assumptions had to be made regarding costs for employers, and patients' and their families' expenditure on transport, since no data were available for the Portuguese population. Employers' costs were based on the cost per hour reported by the Portuguese Institute of Statistics [INE] while transport expenses were based on a broad estimate of the distance between home and hospital for the general population [26].

### 2.5. Utility data

Utilities were obtained from the literature in a study with 90 patients with colorectal cancer, obtained by interviews using the standard gamble technique, providing utilities adjusted for disease site in terms of colon versus rectum and by stage of disease from stage I to IV [27].

### 2.6. Cost-utility analysis

The primary outcome measure for this economic evaluation was the incremental cost-effective ratio (ICER) between the blood genetic testing of polymorphisms in COX-2/$PGE_2$ pathway versus no screening. Costs are included in the numerator and effectiveness in the denominator in terms of quality-adjusted life years (QALY). Willingness to pay was set at 50,000 US Dollars/QALY, as is usual in most economic analyses, and converted to euros (€) at a 2015 exchange rate to give a value of €44,870/QALY [28,29]. Another possibility for this controversial point could be to adopt a threshold of twice the gross national income per capita as suggested by some institutions [30–32]. For Portugal that option would return a similar value: USD 42,640 or €38,270 after conversion. To allow comparability with other similar published studies we adopted the same €44,870/QALY (USD 50,000) threshold.

Data on the transition probabilities and range for both costs and outcomes are provided in a supplementary table.

According to the model, cost-avoidance is expected if patients are diagnosed in earlier stages of disease after a positive genetic test is followed by follow-up colonoscopies, which would start much earlier than the current recommendations for the general population (see CRC stages variables in the supplementary table). Moreover, efficacy would be better for patients without colorectal cancer, due to the removal of adenomas (incidence reduction), and those with colorectal cancer diagnosed at earlier stages, who would undergo less invasive treatments (improved quality of life) and with better survival rates (mortality reduction) [33,34].

Every point estimate is accompanied by a range and a distribution to account for variability and allow sensitivity analysis, using deterministic and probabilistic approaches. For sensitivity analysis, when only a single value was available in the literature, that value was used for the base case and the range was calculated for a 10% deviation (5% below and 5% above the central value). This applied mainly to costs which are usually given by a single value in the literature [60]. For probabilistic analysis, all distributions had to be calculated using an approximation of the mean and standard deviation (SD) provided by the TreeAge software. For transition probabilities, beta distributions were used with an alpha of (mean$\hat{2}$)*(1-mean)/(SD$\hat{2}$) and a beta of ((mean*(1-mean)/(SD$\hat{2}$))-((mean$\hat{2}$)*(1-mean)/(SD$\hat{2}$)), and for costs gamma distributions were used with an alpha of (mean$\hat{2}$)/(SD$\hat{2}$) and a lambda of mean/(SD$\hat{2}$).

Expert opinion was sought in both the medical and economics areas for building the model and gathering the best available data, but not for estimating any parameter.

## 3. Results

The results of the model for the base case scenario, comparing the COX-2/$PGE_2$ pathway genetic testing strategy versus no genetic screening are presented according to four different increased CRC risk assumptions, namely 1.5, 2, 3 and 5 times the average risk and also for two different prices, €10 and €30 as shown in Table 1.

The results show that for the threshold of €44,870/QALY considered in our population, only the options within the assumption of an increased susceptibility of 5 times provided by the screening test would have cost utility. For a 5-fold increased risk of CRC provided by a positive test, the cost-effectiveness for a €30 test would be €44,356/QALY and for a €10 test would be €30,389/QALY. If a positive test provided increased risks of only 1.5–3 times, then all strategies would overcome the threshold, no matter what price the screening test is.

**Table 1**
Results of the cost-effectiveness model for the base case scenario.

| CRCRisk | Strategy | Cost (€) | Incremental Cost (€) | Effectiveness (QALY) | Incremental Effectiveness (QALY) | Cost Effectiveness (€/QALY) | ICER (€/QALY) |
|---|---|---|---|---|---|---|---|
| | No test | 237 | | 0.9937 | | 238 | |
| 1.5× | Genetic test 30€ | 354 | 117 | 0.9940 | 0.0003 | 356 | 408,387 |
| | Genetic test 10€ | 333 | 97 | 0.9940 | 0.0003 | 336 | 338,548 |
| | No test | 308 | | 0.9918 | | 310 | |
| 2× | Genetic test 30€ | 411 | 104 | 0.9924 | 0.0006 | 414 | 180,868 |
| | Genetic test 10€ | 391 | 84 | 0.9924 | 0.0006 | 394 | 145,948 |
| | No test | 379 | | 0.9900 | | 383 | |
| 3× | Genetic test 30€ | 469 | 90 | 0.9908 | 0.0009 | 473 | 105,028 |
| | Genetic test 10€ | 449 | 70 | 0.9908 | 0.0009 | 453 | 81,749 |
| | No test | 521 | | 0.9862 | | 528 | |
| 5× | Genetic test 30€ | 584 | 64 | 0.9876 | 0.0014 | 592 | 44,356 |
| | Genetic test 10€ | 564 | 44 | 0.9876 | 0.0014 | 571 | 30,389 |

CRC, Colorectal Cancer; QALY, Quality Adjusted Life Years Saved; ICER, Incremental Cost Effectiveness Ratio.

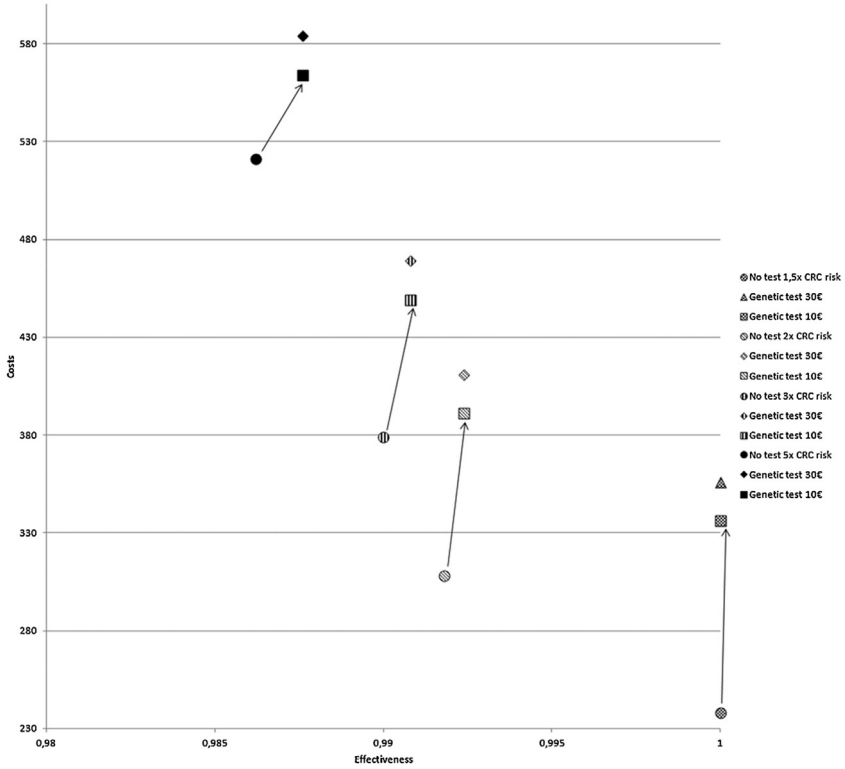


**Fig. 2.** Cost utility analysis of genetic test screening versus no screening according to three assumptions of increased colorectal cancer (CRC) risk and different costs. The x-axis represents the effectiveness in quality-adjusted life years (QALY) and the y-axis represents the cost in euros (€). The cost-effectiveness frontiers are represented by the black arrows between the options of no screening test (circles) and the best option with same effectiveness for lower cost (squares) for the same assumption of increased risk (same colour). Strategies for a less costly genetic test are the best cost-effectiveness options, but while for assumptions of an increased CRC risk of 1.5–3-fold the incremental cost-effectiveness ratios are above the adopted threshold of €44,780/QALY, the only strategies that stay below the threshold are for an assumption of an increased risk of 5×, providing incremental cost effectiveness ratios (ICERs) of €44,356/QALY for a €30 test and €30,389/QALY for a €10 genetic test.

The plot of the four risk assumptions comparing genetic screening versus no screening is given in Fig. 2. The cost-utility frontiers are indicated by the black arrows between the options of no screening test (circles) and the best option (same effectiveness for lower costs) for the same assumption of increased risk (same colour).

Deterministic sensitivity one-way analysis, representing the influence of each variable on the ICER is shown in Fig. 3 as a tornado diagram. Only 11 of all the included variables are listed, from the most influential parameters at the top to the least influential ones at the bottom, and variables not shown had even less influence on the ICER. The variables that most influenced the ICER were the rate of a positive genetic test among the population and its cost, the proportion of colon versus rectal cancers, the uptake of anaesthesia for colonoscopy in the population and the effectiveness of screening in improving stages of disease between non-screened and screened patients.

The Monte Carlo probabilistic multi-way analysis result for the options of a €30 and €10 genetic test and an assumption of a 5-fold increased CRC risk is displayed in Fig. 4 as an ICER scatter plot. For 1000 simulations represented by each dot and a threshold of €44,870/QALY the analysis shows that the option for the genetic test screening had a cost utility of 47% and 75% of cases, respectively with a discount of 3% represented by all points on the right-hand side and below the dotted line of the willingness-to-pay threshold.

## 4. Discussion

CRC is particularly suitable for prevention since its natural history with a long latency period provides an excellent window of opportunity for early detection [35]. Nevertheless, a considerable proportion of patients with CRC are still diagnosed in the later stages of disease, possibly due to a low compliance with current screening guidelines or an unsuitability of current guidelines whereby they might not reflect the underlying risks of target populations [3].

The shift towards a personalized medicine era has highlighted the importance of exploring the genetic background as causal variations underlying complex diseases with the potential for targeting screening, instigating chemoprevention, improving outcomes and decreasing costs of care [9,36–41]. Genetic testing has already been explored and found to be effective and economically viable in specific settings, mostly in the fields of chemoprevention and pharmacogenomics [36–41].

Here, we report an economic evaluation on a genetically targeted screening strategy for CRC, illustrated by polymorphisms in COX-2/$PGE_2$ pathway genes. In our original article we reported a panel of seven tag SNPs in four $PGE_2$-related genes (*COX-2/HPGD/SLCO2A1/ABCC4*) as risk biomarkers for the development of CRC, with risk estimates ranging from 1.5 to 2.0 and genotypic frequencies between 3 and 60% [7].

The hypothetical model was designed by establishing a parallel with the screening recommendation for individuals with a first-degree relative who has had CRC [42]. In this setting the screening schedule is anticipated a decade by starting at age 40 because of their above-average inherent risk of two to three times for CRC onset [42][73]. The fact that 445 polymorphisms are known does not mean that all are relevant in terms of increased risk for the disease. A screening test should only be done for those polymorphisms that are related to an above-average increased risk of this magnitude, which should only happen for a few of them and even though the cost would have to be quite cheap as provided by our model conclusions.

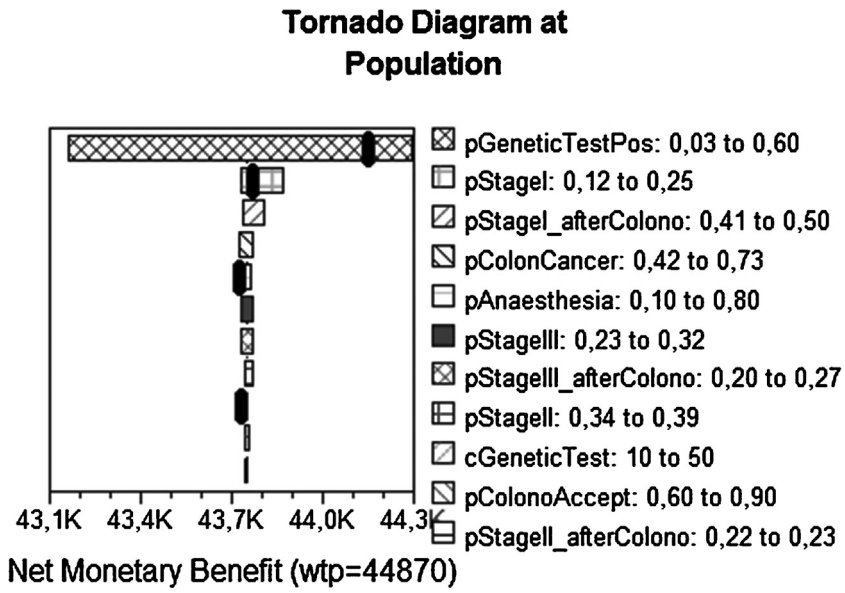


**Fig. 3.** Tornado diagram for deterministic one-way sensitivity analysis. Variables tested in one-way sensitivity analysis are displayed on the y-axis while the dotted line on the x-axis represents the base case value in terms of net monetary benefit in euros for a willingness to pay (WTP) of €44,870/QLY, with variables having the widest range for the final result with a wider line at the top. Variables are followed by the values of their analytical range. Variables not displayed varied even less from the result of the model. c, cost; K, thousand; p, probability.

As our model showed, the most cost-effective strategy to target individuals for tailored screening involves the genetic testing of variants conferring at least five times the average risk for a cost not exceeding €30. Although we adopted a conservative expenditure estimate ranging between €10 and €50, in our original epidemiological study the cost for polymorphisms genotyping stayed below €10, using the MassARRAY iPLEX Gold technology that allows the characterization of up to 40 SNP [7]. At the prohibitive prices of commercially available test kits for biomarkers already in use for CRC treatment, in particular the KRAS mutation for predicting the response to EGFR-targeted therapy (€111), the model loses its cost-effectiveness regardless of risk estimates [43].

The ICER under these conservative options of 5 times the increase CRC risk at €10 per test cost was €30,389/QALY for a €44,870/QALY threshold, thus keeping its cost-effectiveness in 75% of simulations according to the model's probabilistic analysis.

On the other hand, when comparing to colonoscopy as a screening option, the prices are totally different (€30 for a polymorphism screening vs. €258 for a colonoscopy under sedation in the model) and the issue of adherence is very relevant because people are used to take blood samples quite easily while the adherence rate to colonoscopy as a screening option is just around 18–38% [44,45].

As already mentioned, the top risk estimate that we reported for a tag SNP was slightly above 2-fold [7]. Since the late 1990s hundreds of genetic variants have been studied in the context of CRC development [8]. Less than 10% (n = 39) presented some degree of credible association, almost exclusively of low predictive value (OR < 1.5), with only two exceeding the 3-fold enhanced susceptibility, as reported in the meta-analysis and field synopsis developed by Theodoratou and colleagues [8]. This being so, it is highly unlikely that a single-locus approach could achieve the desirable overall genetic predisposition for a cost-effective strategy in personalized screening for CRC. The common disease-common variant (CD–CV) hypothesis predicts the involvement of several genetic polymorphisms with small additive or multiplicative impact on complex polygenic diseases [9,46,47]. Furthermore, common diseases such as cancers and cardiovascular diseases are believed to also arise due to a combined effect of genetic and environmental factors [48,49]. Therefore, future studies should explore the effects of possible gene-gene and gene–environment interactions in an attempt to define moderate risk profiles that would represent a cost-effective approach for targeted screening. Houlston et al. [50], in a combined analysis of genome-wide association data, reported a 10-fold increased risk for subjects with ≥15 risk locus versus those with ≤4 risk alleles, with a per allele OR of 1.16. It is expected that 300 independent risk alleles will be needed to formulate a predictive genomic profile that explains the entire genetic component of CRC, and 140–160 to capture 80% of future cancers in the 50% of individuals at greatest genetic risk [10]. In our observational study we found that the best four-locus interaction model, including polymorphisms in *HPGD*, *SLCO2A1* and *ABCC4*, was associated with a 5-fold increased risk for CRC onset, following a multifactor dimensionality reduction (MDR) analysis [7].

The cost utility analysis, although generally robust to changes in the input variables, was particularly sensitive to the prevalence of positive testing, being cost-effective only for common genetic variations with a frequency of at least 31.5%. For rarer polymorphisms with a rate below 3% an ICER well above the stipulated €44,870/QALY threshold is expected (€232,922/QALY).

Limitations of the present study need to be mentioned. Using a genetic panel of abnormalities can always lead to a false reassurance for those patients whose genetic abnormality is not included in the panel. However, because we are testing the general asymptomatic population at the age of 40 years and this population is not at high risk for CRC, the risk of a false reassurance if a positive genetic abnormality is missing from the panel should be minimal. Although an extensive literature research was performed for the best available evidence of all variables included in the model, it is never possible to establish how close we came to real life possibilities. The utilities used in our study were not from the Portuguese population due to the lack of available data, while ranges and distributions for some variables in the sensitivity analysis are not available in the literature and approximations had to be used. Also, because the model concerns screening for the general population, screening methods for high risk populations are beyond the scope of the present study. Finally, it is crucial to recall that the model was developed for the Portuguese population and adjustments would

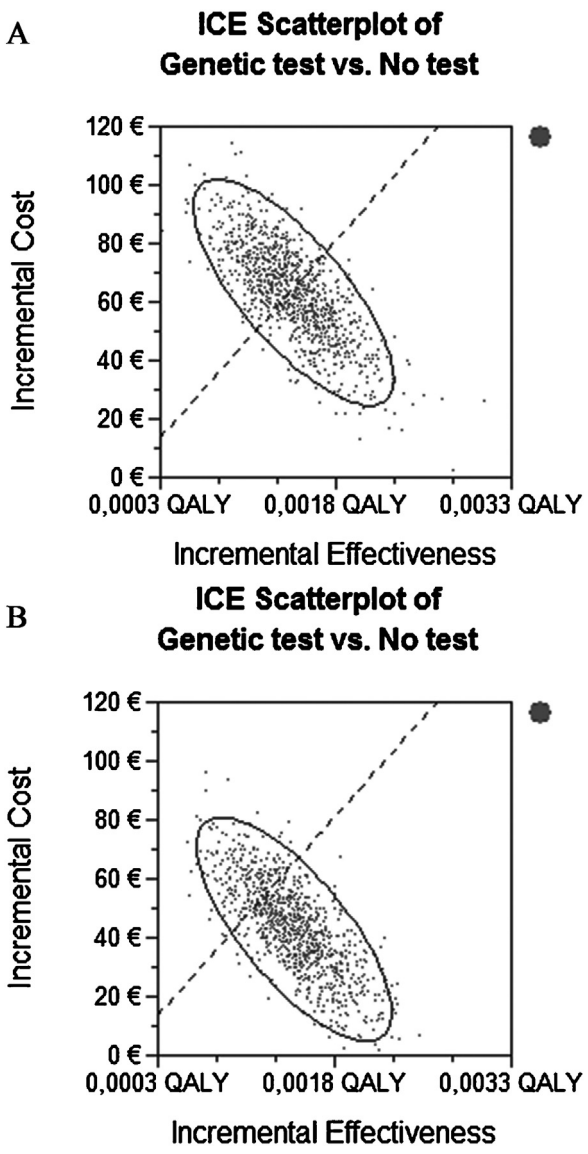


**Fig. 4.** Scatter plot for probabilistic Monte Carlo sensitivity analysis under a 5-fold increase risk assumption for a genotyping cost of (a) €30 and (b) €10. Representation of 1000 simulations where each dot means one simulation, the x-axis represents the incremental effectiveness in terms of quality-adjusted life years (QALYs) and the y-axis represents incremental costs in euros. The ellipse surrounds the estimates that fall within the 95% confidence intervals. Cost-effective simulations are situated below the dotted line representing the willingness-to-pay threshold, set at €44,870/QALY, and comprise (a) 47% and (b) 75% of all simulations.

need to be made for other populations, particularly regarding costs, to evaluate its generalizability.

In conclusion, genetic screening for colorectal cancer has cost utility only under specific assumptions of increased CRC risk and conservative cost estimates, and it could potentially represent a strategy to increase the pool of screened individuals in countries with low adherence to or non-existent population-based screening programmes. Future studies should focus on defining genetic profiles (to achieve significant increase in risk), as single-gene approaches are most unlikely to be cost-effective, given their modest predictive value.

## Conflict of interest

None declared.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.07.012.

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