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ORIGINAL RESEARCH



Cost-effectiveness of a machine learning risk prediction model (LungFlag) in the selection of high-risk individuals for non-small cell lung cancer screening in Spain

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ABSTRACT

Objective: The LungFlag risk prediction model uses individualized clinical variables to identify individuals at high-risk of non-small cell lung cancer (NSCLC) for screening with low-dose computed tomography (LDCT). This study evaluates the cost-effectiveness of LungFlag implementation in the Spanish setting for the identification of individuals at high-risk of NSCLC.

Methods: A model combining a decision-tree with a Markov model was adapted to the Spanish setting to calculate health outcomes and costs over a lifetime horizon, comparing two hypothetical scenarios: screening with LungFlag versus non-screening, and screening with LungFlag versus screening the entire population meeting 2013 US Preventive Services Task Force (USPSTF) criteria. Model inputs were obtained from the literature and the clinical practice of a multidisciplinary expert panel. Only direct costs (€ of 2023), obtained from local sources, were considered. Deterministic and probabilistic sensitivity analyses were performed to assess the robustness of our results.

Results: A cohort of 3,835,128 individuals meeting 2013 USPSTF criteria would require 2,147,672 LDCTs scans. However, using LungFlag would only require 232,120 LDCTs scans. Cost-effectiveness results showed that LungFlag was dominant versus non-screening scenario, and outperformed the scenario where the entire population were screened since the observed loss of effectiveness (-224,031 life years [LYs] and -97,612 quality-adjusted life years [QALYs]) was largely offset by the significant cost savings provided (€7,053 million). The resulting incremental cost-effectiveness ratio (ICER) for this strategy of screening the whole population versus using LungFlag was €72,000/QALY, showing that LungFlag is cost-effective. Various were described, such as the source of the efficacy or adherence rates, and other limitations inherent to cost-effectiveness analyses.

Conclusions: Using LungFlag for the selection of high-risk individuals for NSCLC screening in Spain would be a cost-effective strategy over screening the entire population meeting USPSTF 2013 criteria and is dominant over non-screening.

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1. Introduction

Lung cancer (LC) is the most frequent cause of cancer-related deaths worldwide¹. According to estimates from the World Health Organization's (WHO) Global Observatory on Cancer², approximately 2.2 million new cases of LC were diagnosed in 2020 (11.4% of all cancer diagnoses) and 1.8 million deaths could be attributed to the disease worldwide (18.0% of all

cancer deaths)³. In Spain, LC was the leading cause of cancer death in 2021, causing 22,438 deaths (19.74%)⁴.

Approximately 90% of LCs are smoking related and non-small cell lung cancer (NSCLC) is the most common histological type, accounting for 85%-90% of cases^{5,6}. Other risk factors associated with LC include age, environmental exposures, and comorbidities. Patients with NSCLC are frequently diagnosed at

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advanced stages, when there are no curative treatment options, and therefore have a poor prognosis and a low 5-year survival rate^{7,8}. According to the WHO, 30% of NSCLC patients can be cured if diagnosed and treated early⁹. Therefore, LC detection at an early stage would dramatically reduce mortality, especially in high-risk populations such as heavy smokers^{10,11}.

The National Lung Screening Trial (NLST) and the Dutch-Belgian Lung Cancer Screening trial (NELSON) have shown that LC-specific mortality can be reduced by 20-24% using low-dose computed tomography (LDCT) screening in high-risk populations¹². Likewise, the International Early Lung Cancer Action Program (I-ELCAP) study showed that screening with LDCT improved early LC detection¹³. In order to avoid high false positive rates, overdiagnosis, unnecessary exposure to radiation, and limit the economic burden of screening, ideally LDCT should be offered to high-risk individuals rather than the usual screening population¹⁴.

Strategies to identify target populations for LC screening can be divided into two categories: eligibility based on age and smoking history standard criteria and risk prediction models (RPMs) which allow the calculation of personalized risk taking into account additional risk factors¹⁵.

Comparative studies have shown that strategies using solely age and smoking history as standard criteria may be inferior to strategies involving personalized risk calculation because they exclude other known risk factors for LC^{16,17}. To address this limitation, several LC RPMs like the Prostate Lung Colorectal and Ovarian risk prediction model (PLCOM2012) or the Liverpool Lung Project risk model (LLPv2), have been developed based on established risk factors such as smoking, occupational exposure, family history of LC, and respiratory disease^{10,14}. Moreover, the CanPredict (lung) model has been developed recently in the UK in order to calculate personalized risk using information derived from the primary care electronic health records¹⁸. One of the most widely used lung screening guidelines, the US Preventive Services Task Force (USPSTF) 2013, recommended annual screening for LC with LDCT in adults aged 55 to 80 years with a 30 pack-year smoking history who continue to smoke or quit within the past 15 years. Current recommendations were revised in 2021 by lowering the starting age of screening to 50 and reducing the required number of pack-years to 20¹⁵.

Artificial intelligence (AI) and machine learning have emerged as new tools for assessing large amounts of medical data by using complex algorithms and software, bringing new opportunities for improving LC screening methods, and some studies have shown that the use of an AI-based system in the initial LDCT of LC screening is cost-effective^{19,20}. LungFlagⁱ is a machine learning-based NSCLC RPM, evaluating routine clinical and laboratory data to improve selection of individuals at-risk for enrollment in LC screening programs. LungFlag works with variables that are of common use in lung cancer screening programs (age, sex, smoking status) and of typical routine health checks (e.g. blood exams)²¹. Gould et al. describes its development and validation using up to 834 clinical parameters through a machine learning process. LungFlag is a more accurate RPM for the early diagnosis of NSCLC compared to the use of standard eligibility criteria or predictive models such as PLCOM2012^{21,22}.

The aim of this study is to assess the cost-effectiveness of implementing LungFlag RPM in Spain for the identification of individuals at-risk for enrollment in NSCLC screening programs, compared to the current situation in Spain where no LC screening is performed, and compared to a hypothetical scenario where the entire population meeting USPSTF criteria would be screened without using any RPM to select high-risk patients.

2. Methods

The cost-effectiveness analysis (CEA) was performed using a global pharmacoeconomic model adapted to the Spanish setting according to guidelines for health technology assessment in Spain and international recommendations^{23,24}. To this end, a multidisciplinary panel of experts - composed of two oncologists, two pulmonologists, one thoracic surgeon, one radiologist, one epidemiologist, and one primary care cancer researcher - validated the assumptions made, the model parameters, and the clinical feasibility of the results through a written questionnaire completion, a face-to-face advisory board event and subsequent virtual meetings.

The global model was developed following international recommendations^{25,26}, and the analysis was performed according to the economic evaluation guidelines and the CHEERS checklist²³ (Table S7, Supplementary Material).

2.1. Model structure

A combination of a short-term decision-tree and a long-term Markov model was used to assess the effectiveness and the costs associated to selecting high-risk individuals for screening with LDCT with LungFlag RPM versus:

- screening the entire target population meeting USPSTF criteria with LDCT without using any RPM (screening without RPM).
- non-screening (current situation in Spain).

The decision-tree was developed to capture the first stage of the clinical pathway, in which the target population followed a predetermined path based on whether cancer was present and at what clinical stage, the sensitivity and specificity of the algorithms and scans, and adherence to LDCT screening. In addition to the decision-tree, a 4-health state (no cancer, undiagnosed NSCLC, diagnosed NSCLC and death) Markov model with monthly cycles was used to capture the remainder of the clinical pathway and to assess the long-term clinical and economic outcomes, where undiagnosed individuals will ultimately receive a symptomatic diagnosis or not depending on the presence or not of a screening program (Figure 1).

Individuals in the non-screening arm without cancer moved to the 'no cancer' health state in the Markov model, and those who had cancer, entered the Markov model in the 'undiagnosed NSCLC' states.

Individuals in both screening arms (screening with LungFlag and screening without RPM), who were found to have cancer, were split across the different cancer states (either had a true positive (TP) or false negative (FN) finding), determined using algorithm-specific sensitivity and specificity data (see below). If

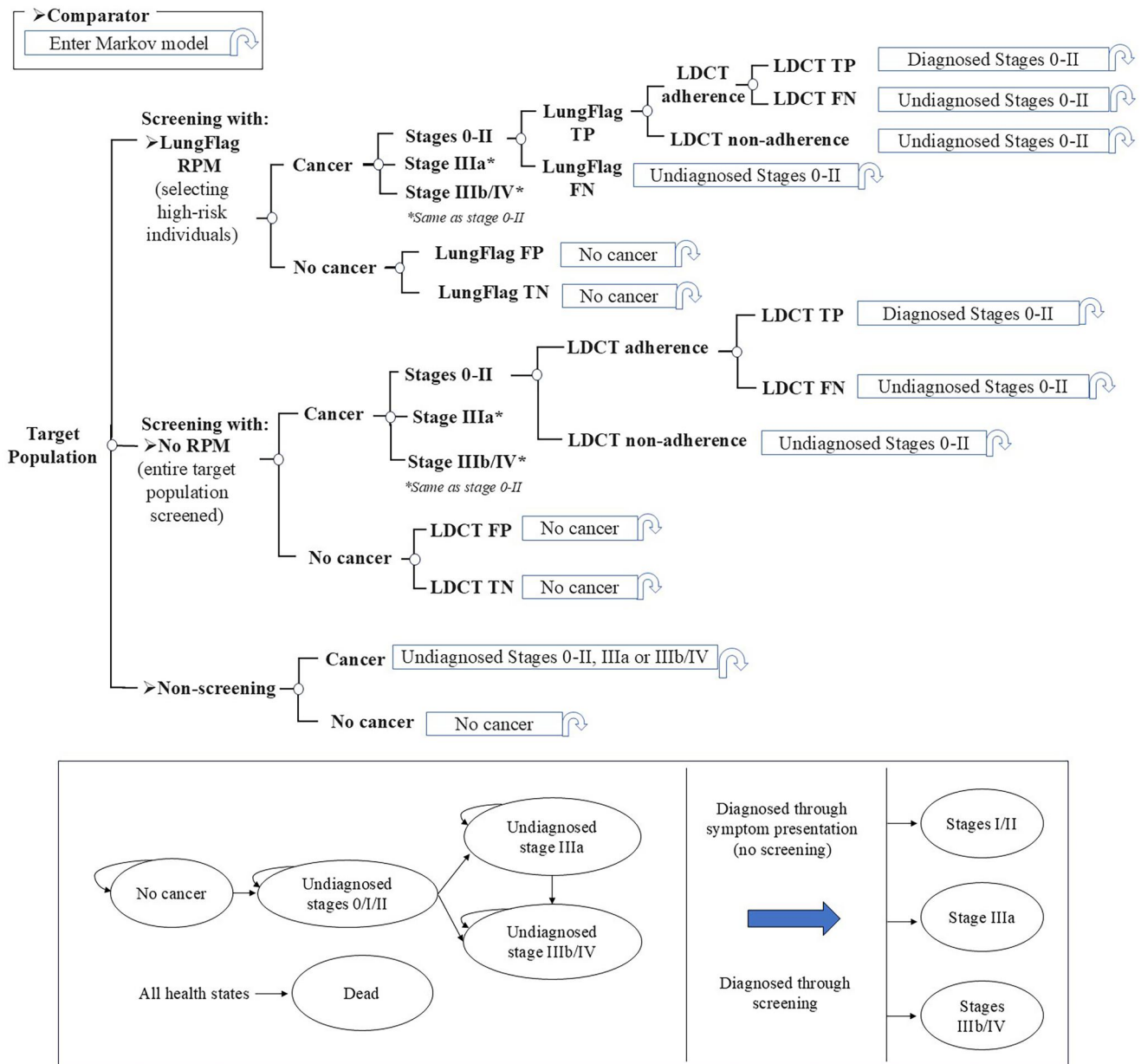


Figure 1. Model diagram.

RPM: risk prediction model; LDCT: low-dose computed tomography; TP: true positive; FN: false negative; FP: false positive; TN: true negative

the individual did not have cancer, they entered the 'no cancer' state, but those who received a false positive (FP) flag with LungFlag still accrued LDCT costs. Individuals who did not adhere to LDCTs, remained in the 'undiagnosed NSCLC' state. People in the health states of 'undiagnosed cancer' or 'no cancer' were annually re-assessed throughout the time horizon of the analysis.

Individuals starting the Markov model without cancer had the probability of getting cancer throughout the time horizon. Once people were diagnosed with cancer and moved to the diagnosed cancer states (Figure 1), where they remained (absorbing states), accruing costs, life years (LYs) and quality-adjusted life years (QALYs) in accordance with the cancer stage at diagnosis. Transition probabilities between health states represent the natural history of the disease in the general population and were obtained from Hinde et al.²⁷ (Table S1, Supplementary Material).

2.2. Model settings and target population

The analysis was conducted from the perspective of the Spanish National Health System (NHS) and, therefore, only direct medical costs were considered. A temporal horizon of 50 years was set, which is considered sufficiently long to reflect relevant differences in health outcomes that take place over the patients' lifetime. A 3% discount rate was applied for both costs and future effects (LYs and QALYs), in accordance with published recommendations on the evaluation of health technologies in Spain²⁸.

The target population of the analysis was defined as those individuals meeting 2013 USPSTF screening criteria (as described above) in Spain. This target population was estimated at 3,835,128 subjects (Table S2, Supplementary Material), according to data published in the National Health

Survey²⁹ and considering tobacco consumption by age group, the number of cigarettes consumed per day by daily smokers and the time since quitting smoking by former smokers (Table S3, Supplementary Material). The gender distribution was adjusted to the age range of the Spanish population³⁰.

For all comparators, the probability of having cancer was estimated according to the following parameters: the 5-year prevalence of the general Spanish population of 139.3/100,000 inhabitants², the increased relative risk of 24.11 for being an active smoker or having a smoking history³¹ and NSCLC accounts 82.5% of all LCs³².

2.3. Clinical inputs

2.3.1. Screening and diagnosis of NSCLC

In the non-screening arm, individuals who had cancer entered in the 'undiagnosed NSCLC' states according to the following distribution by stages validated with the experts and aligned with literature³³: stages 0-II (19.1%), stage IIIa (15.8%) and stages IIIb/IV (65.1%).

In both screening arms (screening with LungFlag and screening without RPM), individuals were split across the different cancer stages, albeit with the following distribution established by the experts, who considered that significantly more patients are diagnosed at early-stages: stages 0-II (75%), stage IIIa (7.5%) and stages IIIb/IV (17.5%). This distribution is in line with published LC screening studies^{34,35}.

Sensitivity and specificity for LungFlag were obtained from the retrospective case-control study by Gould et al.²¹, considering different time windows before clinical diagnosis. The 90-365 days' time window was chosen because we believe that patients were unlikely to present symptoms or clear signs of lung cancer 90 days before diagnoses. In a meta-analysis, median onset time for LC symptoms was reported to be 41-143 days³⁶. Table 1 shows LungFlag sensitivity obtained for each stage for a target specificity of 90% (base case)²¹ and also for the sensitivity analysis. Sensitivity calculation of LungFlag was established by the cases clinically diagnosed in the flagged population, thereby, incorporating both the sensitivity of the RPM and the diagnosis process (LDCT). For the 'screening without RPM' arm, where the entire target population is screened, 85% specificity and 93.1% sensitivity for LDCT was assumed³⁷.

For both screening scenarios, a 56% adherence rate to LDCT was considered in the base case³⁵.

Table 1. LungFlag sensitivity and specificity rates. These values include LDCT specificity and sensitivity.

NSCLC stage	Specificity		Sensitivity	
	Base case	SA	Base case	SA
Stages 0-II	90.1%	95.1%	44.1%	30.1%
Stage IIIa	90.0%	95.0%	42.6%	26.0%
Stages IIIb-IV	90.1%	95.0%	32.8%	20.9%

SA: sensitivity analysis; NSCLC: non-small cell lung cancer.

2.3.2. Mortality and utilities

Age and gender adjusted all-cause mortality data were sourced from Spanish life Tables³⁸ and used to estimate monthly probabilities of general population all-cause mortality. Median overall survival for diagnosed stages 0-II and IIIa was used to calculate the monthly probability of death and therefore estimate the LYs, obtained from the literature^{39,40} and validated by the panel of experts; from this monthly probability the lifetime discounted LYs were calculated. For stages IIIb/IV lifetime discounted LYs were obtained from the recent economic evaluation published by Arriola et al.⁴¹. One-off lifetime discounted LYs are shown in Table 2.

The model considers that, after diagnosis and treatment of NSCLC at early stages, a proportion of patients are cured. It was assumed that a patient diagnosed with early-stage NSCLC is considered clinically cured when he/she is free from disease five years after completing treatment. Conservatively, the current cure rate was estimated at 32% for stages 0-II and 21.5% for stages IIIa³⁹.

Utility values, which represent the product of the quantity and quality of life and range from 0 (death) to 1 (full health), were also obtained from the literature and validated by the panel of experts. People who were in the no-cancer and the undiagnosed cancer stages were assumed to have no negative impact on their quality of life, meaning that these people had general population utility values. Lifetime discounted QALYs for stages 0-II and stage IIIa were calculated in the same way as LYs applying the Spanish utility values described above, and for Stages IIIb-IV they were obtained from Arriola et al.⁴¹ (Table 2).

2.4. Healthcare resources

Healthcare resource consumption was agreed upon by the panel of experts and is shown in Table 3. In the model, costs of diagnosis and treatment were estimated as one-off costs applied to newly diagnosed cancer population at the time of diagnosis. These data were obtained from published Spanish studies and databases^{42,43}.

2.5. Unit costs

Unit costs of the different healthcare resources were obtained from the national healthcare database eSalud⁴⁴ and one-off treatment costs were obtained from the literature^{42,43}, both expressed in euros of 2023 (Table 4).

Table 2. Lifetime discounted LYs and QALYs used in the model, by NSCLC stage.

NSCLC stage	Lifetime discounted LYs*		Lifetime discounted QALYs	
	Cured	Uncured	Cured	Uncured
Stages 0-II	29.37	9.87	16.35	6.89
Stage IIIa	29.37	5.75	16.34	4.50
Stages IIIb-IV	n/a	2.76	n/a	1.90

*Stages 0-II and IIIa uncured LYs were estimated using the median survival for those cancer stages^{35,36}. Cured LYs for these stages were estimated using the all-cause mortality probability³⁴.

LYs: life years; QALYs: quality-adjusted life years; NSCLC: non-small cell lung cancer.

Table 3. Use of healthcare resources.

Type of Healthcare Resources	Consumption	
	% of patients	Frequency
NSCLC screening with LDCT (with or without RPM)		
LungFlag RPM	100%	Annually
Primary Care visit	100%	Annually*
LDCT scan	100%	Annually*
Pneumology consultation visit	100%	Annually*
Clinical diagnosis of NSCLC**		
PET/CT scan	100%	One-off (newly diagnosed)
Specialist visit	100%	One-off (newly diagnosed)
Biopsy	70%	One-off (newly diagnosed)
Bronchoscopy	55%	One-off (newly diagnosed)
Emergency visit	50%	One-off (newly diagnosed)
Primary Care visit	50%	One-off (newly diagnosed)
Treatment of NSCLC***		
Stages 0-II		
Thoracic surgery	88%	One-off (newly diagnosed)
Radical radiotherapy or SBRT	12%	One-off (newly diagnosed)
CT scan + oncologist visit (follow-up)	100%	Up to year 5
Pneumologist visit (follow-up)	100%	Up to year 5
Stage IIIa		
Potentially curative treatment	60%	Same as stage 0-II
Palliative treatment (see Table 4)	40%	One-off (newly diagnosed)
Stages IIIb/IV		
Systemic cancer therapy (see Table 4)	100%	One-off (newly diagnosed)

*Only those patients adherent to LDCT.

**Patients diagnosed with cancer following a true-positive or false-positive LDCT.

***Patients with cancer diagnosed with screening program or through symptom presentation, by stage.

LDCT: low-dose computed tomography; PET: positron emission tomography; CT: computed tomography; SBRT: Stereotactic body radiotherapy; NSCLC: non-small cell lung cancer; RPM: risk prediction model.

Table 4. Unit costs used in the model.

Healthcare Resources	Unit Cost (€)	Source
LDCT scan	111.60	39
Primary care visit	25.61	39
Specialist visit e.g: oncologist, pneumologist, etc	97.14	39
Emergency visit	212.85	39
CT scan with contrast	284.95	39
PET/CT scan	606.93	39
Bronchoscopy	248.44	39
Biopsy	238.00	39
Thoracic surgery	1,443.39	39
Radical radiotherapy	4,394.47	39
SBRT	6,420.62	39
Palliative treatment, stage IIIa (one-off cost)	10,085.89	38
Systemic cancer therapy, stages IIIb/IV (one-off cost)	78,642.04	37

LDCT: low-dose computed tomography; CT: computed tomography; PET: positron emission tomography; SBRT: Stereotactic body radiotherapy.

The cost of LungFlag is made up of an annual license fee and an installation fee, and it is expected that 17 licenses would be required for Spain, with a total annual cost of around €60,000. It was assumed that all the information needed to run LungFlag was already available in existing patient records.

2.6. Sensitivity analysis

To assess the uncertainty associated with model parameters as well as to further determine the robustness of the base case results, deterministic and probabilistic sensitivity analyses were performed.

First, alternative scenarios to base case settings were explored. Specifically, a time window of 270-365 days was

considered (instead of 90-365 days in base case), using USPSTF 2021 criteria to define the target population, and a 95% specificity was set for LungFlag (with sensitivity reduced to 30.1%, 26.0% and 20.9% for stages I-II, IIIa and IIIb-IV respectively). Also, a scenario in which adherence to the screening with LungFlag was increased from 56% to 70% was examined, and a scenario in which cure rate for stages 0-II was higher (80%) was also explored. Finally, scenario was explored in which diagnosed NSCLC (stage 0-II and IIIa) patients who are not-cured are assumed to eventually progress to advanced disease and the associated costs are also added.

In addition, a one-way sensitivity analysis (OWSA) was performed by modifying the different parameters to plausible extremes with respect to the base case value. The lower and upper bounds of the parameters are shown in Table S4 of Supplementary Material.

Finally, a probabilistic sensitivity analysis (PSA) was also performed. According to international recommendations, 1,000 simulations were run by second-order Monte Carlo methodology, simultaneously varying the model variables with a given distribution and assuming a standard error of 10% of mean values if the standard deviation is not available⁴⁵. Gamma distribution was used for screening, diagnostic and treatment costs, lifetime utilities, lifetime QALYs, and healthcare resources. Beta distribution was used for demographic data, LC prevalence and adherence rates. A Dirichlet distribution was used in the simulation for the distribution of individuals by cancer stage, the sensitivity and specificity of LungFlag, and the transition probabilities of the Markov model.

3. Results

3.1. Base case

For the target population of 3,835,128 subjects meeting USPSTF 2013 criteria in Spain, in the hypothetical scenario where everyone is screened, 2,147,672 LDCTs scans would be needed assuming a 56% adherence to the screening program. Comparatively, using LungFlag to identify high-risk individuals, only 232,120 LDCTs would be required for the same adherence.

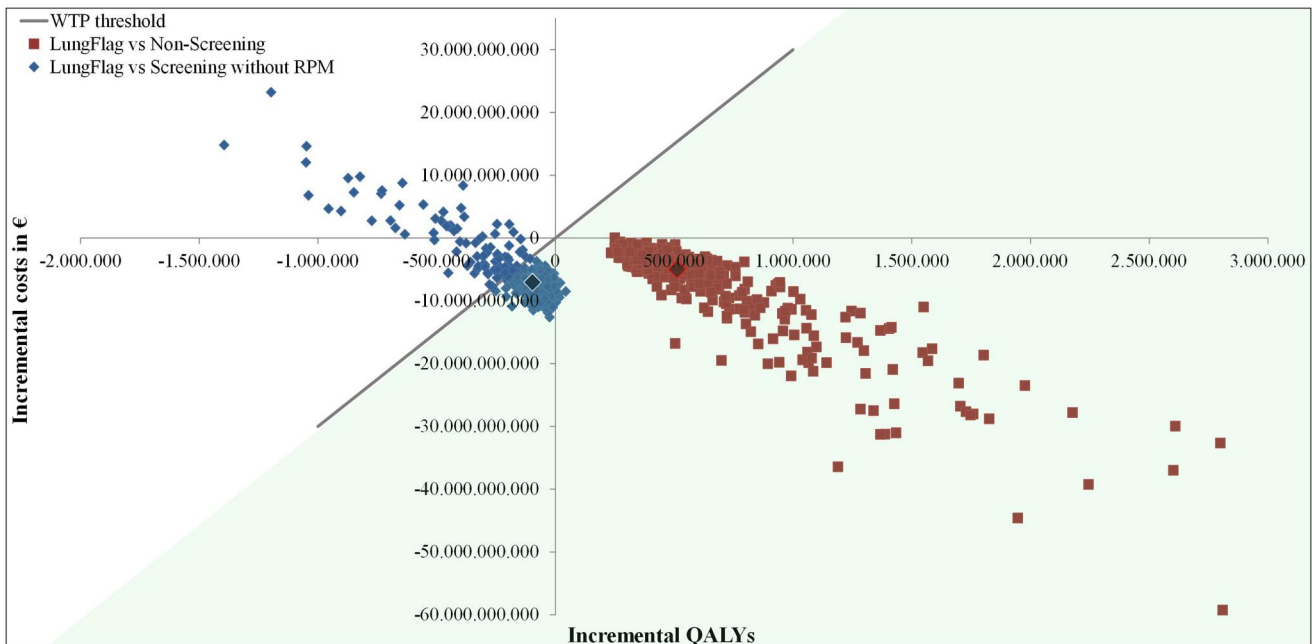
Detailed costs and health outcomes (LYs and QALYs) for the whole target population over the lifetime horizon are shown in Table S5 of Supplementary Material. In Table 5, the three strategies compared were ranked by total cost to estimate the incremental cost-effectiveness ratio (ICER), calculated against the reference strategy (screening with LungFlag). Strategies with lower costs and higher QALYs are highlighted in bold.

The non-screening strategy was dominated by the reference strategy (screening with LungFlag), since it is more expensive and generates fewer QALYs. Comparing the hypothetical scenario in which the entire target population would be screened without RPM versus LungFlag (reference strategy), the effectiveness gain is modest (224,031 LYs and 97,612 QALYs) relative to the substantial incremental cost (€7,052 million). The resulting incremental cost-effectiveness

Table 5. Base case results for the target population, ranked by total cost and ICER calculated versus reference strategy (in bold, lower costs and higher QALYs).

	Total costs	Cost difference	QALYs	QALYs difference	ICER (vs reference)
Screening with LungFlag	€10,053 million	reference	61.66 million	reference	reference
Non-Screening	€15,029 million	+ €4,975 million	61.15 million	−0.512 million	dominated
Screening without RPM	€17,106 million	+ €7,053 million	61.76 million	+0.098 million	72.252€/QALY

RPM: risk prediction model; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio.

**Figure 2.** Incremental cost-effectiveness plane.

QALYs: quality-adjusted life years; WTP: willingness-to-pay

ratio (ICER) indicates that screening the entire target population is not a cost-effective strategy compared to LungFlag (€72,252/QALY), considering the willingness-to-pay (WTP) threshold of €25,000–30,000/QALY commonly accepted in Spain^{46,47}. Therefore, our analysis indicates that screening with LungFlag is the most cost-effective strategy among those compared. Finally, comparing screening without RPM versus non-screening the resulting ICER of €3,410/QALY indicates that screening without RPM is a cost-effective strategy compared to non-screening (more costly and more QALYs).

3.2. Sensitivity analysis

Alternative scenarios to the base case showed consistent results. For all scenario analyses but one, non-screening remained dominated by LungFlag (reference strategy), and screening the entire target population without RPM it remained non cost-effective compared to LungFlag (less QALYs but greater savings) (Table S6, Supplementary Material).

Regarding the OWSA, the variables with the highest impact on the base case ICER were: lifetime QALYs of stages 0-II, the adherence to screening and the sensitivity of LungFlag for stages 0-II. The OWSA results for screening without RPM versus screening with LungFlag (reference strategy) are represented in a tornado diagram (Figure S1, Supplementary Material), and show that the ICER for all the variables tested remains above the WTP threshold of

€25,000–30,000/QALY^{46,47}, indicating that screening without RPM is not a cost-effective strategy compared to LungFlag. In other words, the OWSA results show that LungFlag remains the cost-effective option.

The PSA results are represented with an incremental cost-effectiveness plane (Figure 2), where the ordinate axis represents the incremental costs of reference strategy versus both alternatives, and the abscissa axis represents the incremental QALYs of the reference strategy versus both strategies. In addition, a WTP threshold of €30,000/QALY has been drawn to show graphically that simulations below this threshold (in both the northeast and southwest quadrants, and obviously in southeast [SE] quadrant) are considered cost-effective for LungFlag (in green).

All the simulations versus non-screening landed in the SE quadrant, showing that LungFlag is dominant. Most of the simulations (91.4%) versus screening the entire target population show that LungFlag is a cost-effective strategy considering a WTP threshold of €30,000/QALY (Figure 2).

4. Discussion

Several studies have shown that risk-based screening reduces LC mortality more effectively and efficiently compared with USPSTF recommendations⁴⁸. In particular, LungFlag RPM has a higher accuracy for early diagnosis of NSCLC than either standard eligibility criteria for screening or the PLCom2012^{21,22}.

Screening with LungFlag and screening without RPM were dominant versus non-screening (more QALYs and lower cost) in our model, a finding in line with the extensive literature showing that LC screening is cost-effective^{49,50}. The use of LungFlag RPM to select high-risk individuals appears to be cost-effective versus screening the entire population. First, it should be noted that screening all patients meeting USPSTF criteria would require a large number of LDCTs, and the implementation of these screening programs will have to be adapted to the care capacity of the specific health systems in the country. However, the use of RPM such as LungFlag may not be exempt from some resource consumption, although our analysis assumes that all required data is available. Hence, using RPMs approach could preserve healthcare resources by enriching the screening population with the individuals at highest risk of LC. In other words, the implementation of RPMs is attractive because it may help reduce the economic and health related burdens of screening individuals at lower LC risk¹⁸. However, screening the entire eligible population would achieve slightly more LYs and QALYs but requires significantly more resources and increase the burden of screening related harms to those without cancer. In fact, the ICER of screening the entire eligible population compared to the reference strategy (LungFlag) was €72,252/QALY, indicating that this strategy is not cost-effective compared to LungFlag, considering the WTP threshold commonly used in our country^{46,47}. Spain has not implemented a national LC screening strategy, and only a few pilot programs have been developed⁵¹, so Spanish experience is limited to a few centers such as the *Instituto Valenciano de Oncología* (IVO) and the *Clínica Universidad de Navarra* (CUN). In 2020, the Germans Trias i Pujol University Hospital in Barcelona participated in an experimental LDCT LC screening program affiliated with the International Lung Screening Trial (ILST), in which PLCom2012 and USPSTF 2013 strategies were compared⁵². Additionally, CASSANDRA (Cancer Screening, Smoking Cessation AND Respiratory Assessment), is a multicenter and multidisciplinary Spanish pilot project led by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), which was launched in November of 2023 with the objective of initiating a patient centered national LC screening and respiratory health program combining primary and secondary LC prevention. CASSANDRA incorporates the LDCT as screening tool and aims to provide evidence on LC screening feasibility in Spain, to shape LC screening recommendations in the Spanish National Health System (NHS) in the future⁵³.

A few reports investigating LC screening scenarios in the Spanish NHS have been published, concluding that LDCT based screening could be a cost-effective strategy. For example, a CEA compared a scenario based on the implementation of an LC screening program versus another scenario without screening in Spain, and its results suggested that the implementation would be cost-effective for the Spanish NHS. In the base-case, an increase of 4.80 QALYs per patient was obtained, resulting in an ICER of €2,345/QALY⁸. A cost analysis conducted in Cataluña, highlighted the importance of the participant selection criteria and

recruitment effectiveness in the potential savings of a LC screening program; so that if only a prevalence of 1% is found, then the savings covers less than half of the direct costs of screening, while the savings almost cover costs if a 2.2% cancer detection rate is achieved⁵². Another study confirmed that the cost-benefit ratio of LC screening will break even between 3 and 6 years after launching and will generate cost savings thereafter⁵⁴. However, a recent evaluation conducted by the *Servicio de Evaluación y Planificación del Servicio Canario de la Salud* (SESCS), the *Agencia Gallega para la Gestión del Conocimiento en Salud* (ACIS) and the *Unidad de Asesoramiento Científico-técnico* (Avalia-t), concluded that LC screening may not be cost-effective, so the implementation of a LC screening program with LDCT would require the establishment of optimal selection criteria that define the high-risk population⁵⁰. Controversy regarding the cost effectiveness of screening remains, so it is imperative that further efforts to establish a national LC screening program take this into account⁵¹.

Outside the Spanish context, most studies conclude that screening for LC with LDCT is cost-effective⁴⁹. Results range from US\$18,452 to US\$66,480 per LYs gained and US\$27,756 to US\$243,077 per QALY gained for repeated screening. The results of cost-effectiveness analyses were sensitive to several key model parameters, including the prevalence of LC, the cost of LDCT for screening, the proportion of LC detected as localized disease and the lead time bias⁵⁵. Smoking cessation rates may also influence the cost effectiveness of screening. To our knowledge, our study is unique in analyzing cost-effectiveness using a RPM in Spain to select high-risk individuals for LC screening.

Our study has some limitations. For instance, Markov models are characterized by structural rigidity, hindering a complete representation of usual clinical practice. Long-term analyses are always subject to uncertainties, although we have used the best available sources in the literature for transition probabilities and the rest of the model parameters. Regarding transition probabilities to death, it was assumed that people in health states “No Cancer” and “Undiagnosed” Cancer Stages assume general background mortality, as it was not possible to find a source for undiagnosed cancer specific mortality. A lifetime horizon must be used since costs, LYs, and QALYs for diagnosed cancers are estimated as lifetime values. The one-off lifetime costs, LYs and QALYs obtained from the literature should consider 2023 care standards, which could be subject to change in the future. A further limitation exists concerning lifetime costs, which do not take into account progression costs, although the addition of these costs were explored in a scenario analysis, which did not have a substantial impact on study results. In addition, no utility decrements associated to LDCT scans or treatments have been used in the model, so it is assumed that people without cancer and those undiagnosed have the same utility. Furthermore, the cancer mortality statistics used for the uncured stages 0-II and IIIa NSCLC may not be fully representative, although the best available references, validated by the expert panel, were used. Another limitation concerns the specificity and sensitivity of LungFlag itself,

given that the available evidence comes from a US study^{21,22} and no Spanish specific data exist yet. Also, these data jointly reflect the specificity and sensitivity of the use of LungFlag and subsequent LDCT together, and no data are available for the two interventions separately. It would be interesting to have further studies analyzing the accuracy of LungFlag and LDCT sequentially. Likewise, our analysis does not include the resources and costs associated with the implementation of LungFlag in Spain, as we have assumed that all the data required to run LungFlag are already available, which is a limitation, as in reality additional visits or tests may be needed. Therefore, it would be interesting to conduct an *ad-hoc* study focusing on the implementation of RPMs in lung cancer screening. Finally, according to experts, some model parameters are associated with a high uncertainty, and within-country variability is considerable, such as adherence to screening programs. As lung cancer screening is not implemented in Spain, there is little evidence of real-world adherence, and most studies come from the US, where adherence rates vary widely^{56,57}. For this reason, to overcome this and the other limitations, several sensitivity analyses were carried out.

5. Conclusions

The implementation of the machine learning model LungFlag for the selection of high-risk individuals for NSCLC screening in Spain, would be cost-effective compared to screening all those eligible meeting 2013 USPSTF criteria. The two screening strategies would be cost-effective compared to the current situation of no screening, and LungFlag would even be dominant over non-screening. Further studies are needed to provide local data on the performance of LungFlag in the selection of high-risk individuals for NSCLC, and to validate these results in real clinical practice.

Note

- i. LungFlag is manufactured and owned by Medial EarlySign, 6 Hangar St, Hod Hasharon, 4527703, Israel.

Transparency

Declaration of funding

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Declaration of financial/other interests

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Author contributions

All authors contributed to the study conception and design. JC-T, JB-S, MM, OH, LG, ME-O, VP and LM-S conformed the panel of experts that collected and validated model data and contributed to results interpretation. The first draft of the manuscript was written by MC and DC and all authors commented on previous versions of the manuscript. All authors read and approved the final content of this manuscript.

Previous presentations

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