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## BACKGROUND

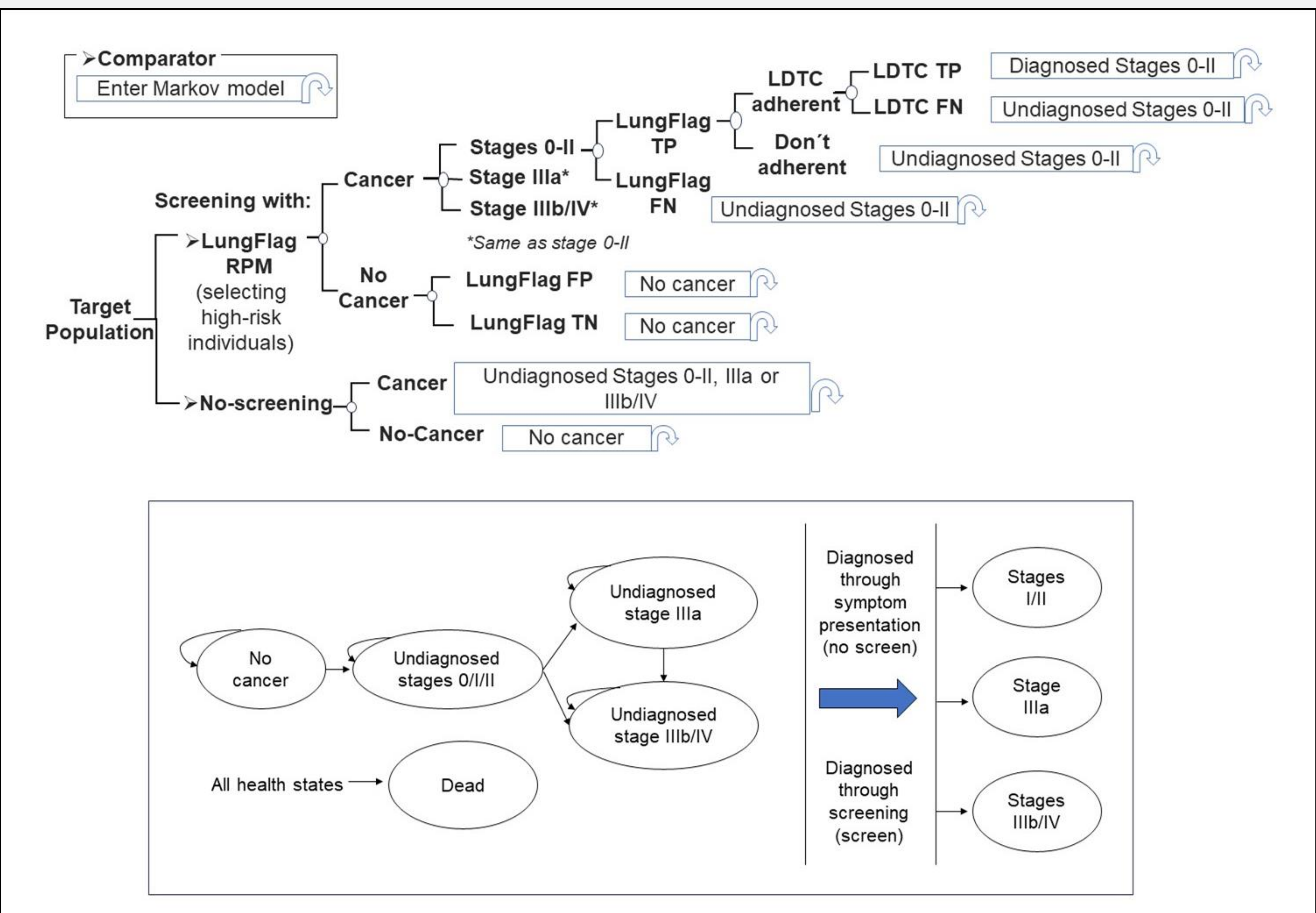
- Several risk prediction models have been developed to select high-risk individuals for lung cancer screening. These allow the calculation of personalized risk as an alternative to standard criteria based on age and cumulative smoking exposure<sup>1</sup>.
- LungFlag™ is an artificial intelligence-based risk prediction model effective in the selection of high-risk individuals by evaluating routine clinical and laboratory<sup>2-3</sup>.
- In Spain, there is no national lung cancer screening program, and only a few pilot programs have been developed<sup>4</sup>.
- The aim of this analysis is to assess the cost-effectiveness of LungFlag™ for the identification of high-risk individuals for enrolment in a NSCLC screening programme in a hypothetical Spanish reference center.

## METHODS

## Model structure

- A joint model combining a decision-tree and a 4-health states Markov model with monthly cycles, was adapted to the Spanish setting (Figure 1).
- The analysis was conducted from the perspective of the Spanish National Health System, so only direct costs were considered.
- A multidisciplinary group of experts validated all parameters and the assumptions made.
- Base case analysis used a 50 years lifetime horizon and a 3% discount rate was applied for both costs and future effects.

**Figure 1. Model diagram**



RPM: risk prediction model; TP: True positive; FP: False positive; TN: True negative; FN: False negative.

- The analysis compared the use of LungFlag™ vs no-screening (current situation in Spain).
- Transition probabilities were obtained from the literature and represent the natural history of the disease in the general population<sup>5</sup>.

## Target Population

Demographic characteristics were in line with those reported by Gould et al<sup>2</sup>. Two hypothetical cohorts of individuals likely to enter the screening programme of a reference center have been defined: a broader cohort of 5,000 ever-smokers (EvSm) aged 45 years (same as Gould et al<sup>2</sup> main cohort), and another cohort of 3,000 individuals fitting 2013 USPSTF criteria (aged 55-80 years and 30 pack/years, also used in Gould et al<sup>2</sup>).

## Parameters

- The probability of having cancer was estimated according to the 5-year prevalence of the general Spanish population (139.3 per 100,000 inhabitants)<sup>6</sup>, the increased relative risk for being an active smoker or having a smoking history (24.11 for USPSTF cohort and 15 for EvSm cohort)<sup>7</sup> and the proportion of NSCLC among all lung cancers (82.5%)<sup>8</sup>.
- Individuals were split across the different cancer stages following the distribution when screening is performed: stages 0-II (75%), stage IIIa (7.5%) and stages IIIb-IV (17.5%)<sup>9-10</sup>. Significantly more patients are diagnosed at early stages. In the no-screening arm, individuals entered in the 'undiagnosed NSCLC' health states according to the distribution observed in studies where diagnosis is made symptomatically: stages 0-II (19.1%), stage IIIa (15.8%) and stages IIIb/IV (65.1%)<sup>11</sup>.
- It was assumed that patient diagnosed with early-stage NSCLC is considered clinically cured if 5 years after treatment they remain disease free.
- An adherence rate to LDCT in the screening program of 56% was considered<sup>10</sup>.
- LungFlag™ sensitivity and specificity were obtained from the retrospective case-control study by Gould et al. For 90% specificity, the sensitivity was 44.1%, 42.6% and 32.8% for stages 0-II, stage IIIa and stages IIIb-IV respectively<sup>2</sup>.

## Healthcare resources and Costs

- Table 2 shows the unit costs (€2,023) of the different healthcare databases and articles<sup>12-14</sup>.

### Table 2. Unit costs used in the model

Healthcare Resources	Unit Cost (€)
LungFlag™ (annual licence)	35,000.00
LDCT scan	111.60
Primary care visit	25.61
Specialist visit (e.g: oncologist, pneumologist, etc)	97.14
Emergency visit	212.85
CT scan with contrast	284.95
PET/CT scan	606.93
Bronchoscopy	248.44
Biopsy	238.00
Thoracic surgery	1,443.39
Radical radiotherapy	4,394.47
Stereotactic body radiotherapy (SBRT)	6,420.62
Palliative treatment, stage IIIa (one-off cost)	10,085.89
Systemic cancer therapy, stages IIIb/IV (one-off cost)	78,642.04

## Sensitivity analyses

- Both one-way sensitivity analysis (OWSA) and probabilistic sensitivity analyses (PSA) were carried out to evaluate the uncertainty associated with the model.

## RESULTS

- As is shown in table 3, for both cohorts screening using LungFlag™ to identify high-risk individuals provides a higher number of LYs and QALYs and significant savings compared to no-screening, therefore it is a dominant strategy versus the current situation in Spain (no-screening).

**Table 3. Results for the case base**

	LungFlag™		No-screening		Incremental	
	EvSm (n=5,000)	USPSTF (n=3,000)	EvSm (n=5,000)	USPSTF (n=3,000)	EvSm (n=5,000)	USPSTF (n=3,000)
<b>LYs</b>	112,36	57,010	111,170	56,320	+1,198	+691
<b>QALYs</b>	98,754	48,232	98,125	47,832	+628	+400
<b>Total costs</b>	€11,874,860	€8,779,473	€15,474,573	€11,756,281	€-3,599,713	€-2,976,808
<b>ICER (€ / QALY gained)</b>					<b>dominant</b>	<b>dominant</b>

- Incremental per patients results showed that the QALYs gain with LungFlag™ was greater in the USPSTF cohort (+0.133) than in the EvSm cohort (+0.126). Also, savings were higher in USPSTF cohort (€-992) compared to EvSm cohort (€-720).
- The OWSA results showed that the dominance of LungFlag™ versus no-screening was maintained for all variables analysed, in both cohorts. Lifetime QALY for stages 0-II, adherence to screening, discount rate for cost and effects, cohort size and LDCT unit costs were the variables that showed the greatest impact (with LungFlag remaining dominant).
- In the PSA, 1,000 simulations were run by second-order Monte Carlo methodology, and 67,2% and 98,6% of the simulations performed showed that LungFlag™ is dominant versus no-screening in EvSm and USPSTF cohorts, respectively.

## CONCLUSION

The implementation of LungFlag™ as a risk model for NSCLC screening in a hypothetical Spanish reference center would be cost-effective compared to no-screening for the 2 hypothetical cohorts analyzed, providing savings and a higher clinical benefit. Narrowing the screening to patients who meet USPSTF criteria seems to optimise the benefits of using LungFlag™

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