Risk-Based Lung Cancer Screening: A Microsimulation Model for the Norwegian high-risk population

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Preface

This thesis follows the research paper format instead of the standard/monograph thesis format. Consequently, Part I of this thesis provides an extended background and the theoretical framework. Part II provides the manuscript in full, including accompanying appendices.

Acknowledgements

A big thank you to those directly involved in my thesis: my supervisor, Emily Burger, for understanding my hunger for ambition, believing in me, and constantly pushing me to do better. My co-supervisor, Natalia Kunst, for sharing her knowledge with me and for the constant feedback, even if remotely. I also want to acknowledge previous students who have studied this topic and were available to help by sharing their work with me, Yansi Wu and Dávid Márk Győrbíró. Then, there's my family; without their support, I could not have been here in Oslo or anywhere else. And my very very precious historical friends, who I enormously miss, together with all my new friends, for always being there for me whenever I needed it, even though we did/will not see each other so much/anymore. And finally, all the incredible people I met along the way, for everything we shared together and the support we gave each other. We had such a great time; I'm glad I can't forget it.

Contents

List of Abbreviations

4ITLR 4-IN-THE-LUNG-RUN. 8, 10, 16

AIC Akaike Information Criterion. 10, 15, 36

BMI Body Mass Index. 16, 38

CPI Consumer Price Index. 11

CT computed tomography. 7, 12, 13, 16

DRG diagnosis-related group. 17

DSA Deterministic Sensitivity Analysis. 11

HUNT Nord-Trøndelag Health. 16

ICER incremental cost-effectiveness ratio. 11, 13, 18

LDCT low-dose computed tomography. 7, 8, 12

LY life-years. 13

MGHITA Massachusetts General Hospital Institute for Technology Assessment. 16

NELSON Nederlands–Leuvens Longkanker Screenings Onderzoek. 7, 8, 12, 17

NLST National Lung Screening Trial. 7, 12, 14–16, 19, 36, 37

PET positron emission tomography. 17

PLCOm2012 PLCOm2012. 16, 38

PSA Probabilistic Sensitivity Analysis. 11, 20

QALY quality-adjusted life year. 8, 10, 13, 18, 19

RCT Randomized Controlled Trial. 7, 8, 12

TIDL Tidlig diagnostikk av lungekreft. 10, 12, 14–16

TSCE Two-Stage Clonal Expansion. 13–15, 18, 20, 34, 37

VDT Volume Doubling Time. 17

VOI Value of Information. 11, 20

Abstract

Purpose. Norway currently has three organized national screening programs; however, due to gaps in capacity and efficiency evaluations, screening for lung cancer is not currently publicly reimbursed. A Norwegian pilot randomized trial is currently underway that involves risk-based management of individuals based on volume doubling time (VDT); however, the cost-effectiveness has not been evaluated. We aimed to develop a microsimulation model and assess the cost-effectiveness of risk-based low-dose CT lung cancer screening strategies in a high-risk Norwegian population to inform policy recommendations in Norway.

Methods. We developed an individual-based natural history model of lung cancer for a population of high-intensity current and former smokers (e.g., $\geq$ 35 cigarette pack-years) aged 40 years over their lifetimes. The model utilized the two-stage clonal expansion (TSCE) model using individual-level data to estimate cancer initiation hazard functions tailored to specific risk profiles based on age and smoking history, allowing for risk stratification. We used a Gompertz function for tumor growth and VDT to inform the risk-stratified management of screening outcomes under the Norwegian pilot-trail screening and management protocols. We projected the discounted (4% per year) long-term costs and quality-adjusted life years (QALYs) for risk-based screening compared with no screening from an extended healthcare perspective, and used NOK 275,000 per QALY gained as a benchmark for cost-effectiveness.

Results. The model projected shifts in lung cancer stage distribution and a reduction in lung cancer mortality attributable to early detection provided by screening. We found that risk-based screening currently under consideration in the Norwegian pilot is likely cost-effective compared to no screening (NOK 129,689 per QALY gained). In a secondary analysis, when we considered alternative eligibility and screening frequencies, we found that the preferred strategy involved narrowing the target ages for the screening eligibility criteria.

Conclusions. Overall, this research supports the implementation of risk-based screening policies in Norway. Further research is necessary to refine the model and incorporate a broader range of clinical data to enhance predictive accuracy and utility for health policymakers and confirm these findings under different scenarios and assumptions.

Part I. Extended background and theory

Background

Lung cancer, which is overwhelming caused by tobacco use, is the leading cause of death from cancer worldwide (18.4% of all cancer deaths), is the most commonly diagnosed cancer (11.6% of all cancers), and causes more deaths than breast, colorectal, and cervical cancers combined [1]. Furthermore, in Europe, it covers the 19.79% of all malignant neoplasms related deaths in EU 27 (27 member states of EU) [2]. Taking a look at the smoking prevalence, it is decreasing in Western countries, however, 17 to 28% of adults currently still smoke, and smoking initiation remains substantial in youths [3]. Lung cancer and other tobacco-related diseases are expected to remain important health problems worldwide for decades [4, 5].

Epidemiology and Risk Factors of Lung Cancer

Lung cancer is a malignant neoplasm originating in the lung, typically developing from cells of the respiratory epithelium [6] and it can be divided into two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC is a highly malignant tumour and accounts for 11% of all lung cancer cases in the UK [7], whereas NSCLC accounts for 88% of the cases. NSCLC can be further divided into (1) adenocarcinoma, (2) squamous cell carcinoma and (3) large cell carcinoma [8]. The most important risk factors are smoking, passive smoking, and environmental risk factors. The risk of lung cancer generally increases with the number of pack-years. One pack-year is the equivalent of smoking one pack (20 cigarettes) per day for one year. Duration of smoking appears to be more important than smoking intensity on the risk [9]. Passive smoking is defined as when a person does not smoke themselves but spends time in an environment where smoking occurs [8] and it causes lung cancer as well, together with respiratory infections and asthma [10]. The overall risk of lung cancer increases when also environmental risk factors coexist, like the exposition to asbestos, silica, and diesel exhaust but also radon gas and air pollution [11]. Lung cancer typically affects older people, mainly men and these are more likely to die from lung cancer than women [5].

Efficacy and Optimization of Lung Cancer Screening Programs

Lung cancer screening aims to enable the early detection of lung cancer to reduce the cancer-related mortality [12]. Historically, chest x-ray alone or in combination with sputum cytology was investigated as a technique potentially enabling population-based lung cancer screening [13, 14]. With the introduction of low-dose computed tomography (LDCT), the interest in an imaging-based lung cancer screening approach was reignited [12]. Nowadays, the standard intervention in screening programs is a LDCT scan, which entails a radiation dose of about 1.5 mSv which is 15 times more than a conventional chest x-ray but more than 4 times less than a conventional chest computed tomography (CT) [15]. LDCT lung cancer screening is the only screening technique that was shown to significantly reduce the lung cancer-related mortality [12]. As a consequence of the fact that virtually no test is completely accurate, the benefits flowing from earlier identification and treatment of lung cancer must be offset by the likelihood that there will be some who may be falsely reassured by false-negative results and a number found to be false positives who will require further investigations and possibly experience additional anxiety relative to the situation in which no screening takes place [8].

Two large Randomized Controlled Trial (RCT)s (the National Lung Screening Trial (NLST) in the United States and the Dutch–Belgian Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) trial in Europe) have found that lung cancer screening with LDCT can reduce lung cancer by 20–24% in high-risk smokers [16, 17], and women may benefit more from screening than men [17, 18]. These studies can help shape the design of definitive large randomised trials [19–21], address knowledge gaps such as recruitment strategies to improve screening uptake [18, 22–26], how to reach lower socioeconomic groups and those who live in underserved areas to decrease disparity [26, 27], optimise screening selection criteria [25, 28, 29] (such as the PLCOm2012 tool, found to be easy to use and took around 5 min to administer, either using a form or electronically (web-based) [30] and the PLCO2012noRace model has been validated in a multiracial population in Chicago [31]), screening frequency and duration [29, 32, 33], nodule management [29], healthcare resource utilisation [29] and cost-effectiveness [24, 27, 29].

Lung cancer screening is most effective when applied to high-risk individuals [34, 35], as screening very low risk individuals has no lung cancer mortality reduction benefit. For example, in the NLST,

individuals who had a 6-year lung cancer risk $< 0.64\%$ had non-significantly more lung cancer deaths in the LDCT group than the comparator group [36].

Is a Risk-Based Lung Cancer Screening Program Cost-Effective in the Norwegian Lung Cancer High-Risk Population?

The objective of this is study is to establish whether a risk-based lung cancer screening program is cost-effective or not, in a Norwegian setting. Lung cancer screening in this specific setting represents an unmet knowledge gap, as no one has ever developed a microsimulation model for it. This is why the study will aim to answer the following research question:

Is a risk-based lung cancer screening program cost-effective in the Norwegian lung cancer high-risk population?

Population-based organised screening programs for breast, cervical and colorectal cancers have been implemented around the world [30], but it is not the same for lung cancer. An organised screening program may have advantages [30], including: provide an evidence-based policy regarding who should be screened; promote screening uptake in general especially in underserved and deprived areas; centralised resources to ease the burden on local authorities [37, 38] and guide participants throughout the entire screening pathway [30].

A literature review is useful to understand what has been done and it was found that Snowsill [8] carried out an extensive clinical effectiveness and cost-effectiveness review. It showed a shift in cancer stage distribution towards earlier stages, which is considered a clinical benefit associated with LDCT screening. And the systematic review of cost-effectiveness analyses done by Snowsill [8] concluded that significant uncertainty remains as to the cost-effectiveness of LDCT screening for lung cancer. They have not produced consistent results in terms of the cost-effectiveness of screening, and certain factors regularly appeared as significant in determining cost-effectiveness: the cost of a LDCT scan, the risk of lung cancer (prevalence, and incidence for studies evaluating more than a single screen) in the screened cohort and the effectiveness of LDCT screening in broad terms (e.g. achieving a stage shift without significant over-diagnosis, extending lung cancer survival beyond lead time, reducing lung cancer mortality) [8]. Importantly, setting specific protocols and resource use are essential to evaluate the cost-effectiveness across countries.

Theoretical Framework

The purpose of economic evaluation is to inform decisions, so the key inputs to any economic evaluation are evidence about the effects of alternative courses of action [39]. It is important to clarify relevant alternatives, specify the perspective assumed, quantify the analysis, and increase the accountability in decision making. It is a comparative analysis of alternative courses of action in terms of both their costs and consequences. Therefore, the basic tasks of any economic evaluation are to identify, measure, value, and compare the costs and consequences of the alternatives being considered. There are different types of economic evaluation, they all have the same measurement of costs in both alternatives, but they differ in the measurement of consequences. Specifically, a cost-effectiveness analysis measures consequences in natural units (e.g. life-years gained, disability days saved, ecc.), a cost-utility analysis uses healthy years (typically measured as quality-adjusted life year (QALY)), and a cost-benefit analysis uses monetary units. The choice in the type of analysis is driven by the Norwegian economic evaluation guidelines [40].

Economic Evaluation and Microsimulation Modelling in Lung Cancer Screening Studies

The optimal setting for an economic evaluation is alongside a clinical trial study in which all cost and effect data are measured in one RCT. The RCT is a widely used study design to measure the effectiveness of health care interventions. Its value is seen as coming primarily as a source of 'internal validity', achieved by randomization because patients will be similar in terms of both observed characteristics which are considered prognostic (i.e. affecting outcomes) and unobserved characteristics (i.e. those that are prognostic but are unknown to the analyst) [24, 39]. With respect to lung cancer screening, the NELSON trial [41, 42] and 4-IN-THE-LUNG-RUN (4ITLR) [43] are some useful RCTs. Data not found in those two trials and that are pivotal trials, can be collected from different published sources and used in one model [44]. In the absence of a comprehensive trial tracking costs and effects, it is possible to take advantage of modelling techniques to simulate the health outcomes and resources consumption of possible strategies. One of the possible and commonly used modelling technique is the individual-based

state-transition (or microsimulation [45]) model. Microsimulation models are implemented because of the ability to more accurately reflect individual clinical pathways, incorporates the impact of history on future events, and more easily capture the variation in patients' characteristics at baseline [46, 47]. It differs from the more traditional deterministic cohort-based models since it simulates the impact of interventions or policies on individual trajectories rather than the deterministic mean response of homogeneous cohorts [48–53]. In a microsimulation model, outcomes are generated for each individual and are used to estimate the distribution of an outcome for a sample of potentially heterogeneous individuals. This individual-level simulation allows the inclusion of stochastic variation in disease progression as well as variation due to individual characteristics, tracking heterogeneous outcomes that can influence future risk of events occurring. Microsimulation models do not require the Markov assumption and so can introduce "memory" to the models' structure. This "memory" characteristic makes microsimulation models more popular in screening programs in which the result of a first screening affects the pathways of the individuals, both in terms of costs and health outcomes.

Tumour Growth Modelling and Statistical Techniques in Lung Cancer Screening Studies

The two-stage clonal expansion (TSCE) model [54] is a commonly used method to estimate tumour initiation. The parameters of the TSCE model are obtained through a likelihood-based method and it can be used to derive incidence functions for smokers and ex-smokers, with specific smoking histories. Once the tumour has developed, it is possible to precisely represent the tumour growth over time.

A Gompertz function for tumour growth is commonly used [55], and it is described as follows:

$$y(t) = y_0 \left(\frac{K}{y_0}\right)^{\exp\left(-\exp\left(\frac{e\cdot\mu_{\max}\cdot(\lambda - t_G)}{\log\left(\frac{K}{y_0}\right)}+1\right)\right)}$$

where:

- $y(t)$ is the predicted size at time t.
- y_0 is the initial tumour size.
- K is the carrying capacity.
- $\mu_{\max}$ is the maximum tumour growth rate.
- λ is the lag time.
- t_G is the time at which growth is evaluated.
- e is the base of the natural logarithm.

The rate of growth decreases as the tumour size approaches the carrying capacity K, according to the term

$$-\exp\left(\frac{e\cdot\mu_{\max}\cdot(\lambda - t_G)}{\log\left(\frac{K}{y_0}\right)}+1\right)$$

of the function.

The term (λ - t_G) essentially controls the timing of the transition from the lag phase (λ - $t_G > 0$) to the exponential growth phase (λ - $t_G = 0$), and eventually to the deceleration phase (λ - $t_G < 0$).

The term $\log(\frac{K}{y_0})$ is a scaling factor that essentially controls how quickly the tumour growth slows down after the exponential growth phase. It's a measure of the relative difference between the carrying capacity and the initial tumour size.

The negative sign in front of the inner exponential function, flips the rapidly increasing function to a rapidly decreasing function and the outer exponential function transforms it into a slowly increasing function. This represents the deceleration phase of the tumour growth as it approaches the carrying capacity K.

Based on the tumour growth rate of the function, it is possible to calculate the volume-doubling time (VDT), which is the time it would take for the volume to double if it continued to grow at the specific rate of growth at that time. In order to get the volume-doubling time it is necessary to solve this equation for t_2:

$$2y_{(t_1)} = y_{(t_1)} \left(\frac{K}{y_{(t_1)}} \right)^{\exp\left(-\exp\left(\frac{e \cdot \mu_{\max} \cdot (\lambda - t_2)}{\log\left(\frac{K}{y_{(t_1)}}\right)} + 1 \right) \right)}$$

where:

- $2y_{(t_1)}$ is the predicted size at time t_2.
- $y_{(t_1)}$ is the initial tumour size at time t_1.
- K is the carrying capacity.
- $\mu_{\max}$ is the maximum tumour growth rate.
- λ is the lag time.
- t_2 is the time at which the volume is doubled.
- e is the base of the natural logarithm.

In R symbolic differentiation can be used, which does not use numerical methods like Newton's method for its computations (computationally demanding), to derive the differential equation analytically and this function can then be numerically evaluated for all the future time steps. The VDT is a key element of the screening strategy and tumour nodule management.

To extrapolate data from the available time frames from the source, to lifetime time horizon, a survival analysis can be used. Different functions make predictions and their extrapolations are compared to find the best predictions. Together with visual inspection, a statistical criterion often used is the Akaike Information Criterion (AIC) value [56], and the function with the lowest value is preferred. It is calculated as follows:

$$\mathrm{AIC} = 2k - 2\ln\widehat{L}$$

where:

- k is the number of parameters in the model.
- $\ln\widehat{L}$ is the natural logarithm of the likelihood function $\widehat{L}$, which is calculated at the estimated parameters.

The AIC helps in balancing the complexity of the model against the goodness of fit of the model. A lower AIC value indicates a better model. The components of the AIC formula are:

- The term $2k$ penalizes the complexity of the model. More parameters can make the model more flexible but can also lead to overfitting.
- The term $-2\ln\widehat{L}$ rewards the goodness of fit. A higher likelihood (or equivalently, a higher value of $\ln\widehat{L}$) indicates a better fit of the model to the data.

Considerations for Economic Evaluations in Healthcare: Perspectives, Costs, and Discounting

The inclusion criterion of the target population is defined as being at high risk of lung cancer. Any definitions of high-risk populations might be eligible in principle since there is wide variation in definitions of high risk between different trials, for instance the specifications from the 4ITLR trial and Tidlig diagnostikk av lungekreft (TIDL) trial. QALYs are the recommended outcome measure for effectiveness [57]. Life-years gained should be reported separately for interventions that has an impact on life expectancy. In the incremental analysis, the outcome can be QALYs gained versus no screening. A lifetime time horizon can be used since it can incorporate all the important future differences in both costs and health effects between alternatives. The time horizon must be such that making it longer would not affect the results in any meaningful way [40].

Which costs and consequences should count, and how they should be measured and valued, depends largely on which of the many different types of decision-makers in health care is intended to be informed by economic evaluation. A broader perspective includes also the costs and consequences falling on other

public agencies, patients, and their families and not only those related to the healthcare sector [39]. Economic evaluations should reflect the setting in which they are being conducted. For instance, the recommendations [57] for economic evaluations of new interventions in the Norwegian health sector imply an extended healthcare perspective. Furthermore, all relevant costs that need to be included and/or excluded, can be found in more specific guidelines [40]. Future costs and benefits must be discounted to reflect the existence of time preference. The amounts spent or saved in the future should not weigh as heavily in program decisions as those spent or saved today [39]. For example, a discount rate of 4% per year (for both health effects and costs) is recommended [57].

Uncertainty and Cost Considerations in Health Economic Evaluations According to Norwegian Guidelines

Following Norwegian guidelines [40], health-related quality of life ((dis)utility values) [58, 59] must, as a rule, be based on generic preference-based measuring instruments. Costs are generally concentrated around the time of diagnosis (when treatment is likely to be initiated) and the time of death (when significant palliative care and medical management costs accrue). Screening costs can be assigned per round and for false positive test results. Norwegian unit costs can be used (NOK), and all costs can be adjusted for inflation using the Consumer Price Index (CPI), when necessary.

To provide a robust and impartial response to the research question, it is important to consider the uncertainty associated with model outcomes [40]. Uncertainty manifests in various forms, necessitating a clear distinction between variability, heterogeneity, and uncertainty. Variability refers to the differences in outcomes experienced by patients with identical baseline characteristics and probabilities, attributable solely to chance [44]. Heterogeneity, on the other hand, pertains to differences between patients that can be partially explained by variations in baseline characteristics.

In modelling studies it is possible to evaluate parameter uncertainty through a Deterministic Sensitivity Analysis (DSA) when a Probabilistic Sensitivity Analysis (PSA) would be too computationally intensive due to the complexity of the model calculations [44]. The DSA involves altering single parameter assumptions to assess their impact on the incremental cost-effectiveness ratio (ICER), while PSA entails simultaneous analysis of multiple parameters, resulting in the calculation of multiple 'new' ICERs. Structural uncertainty is not associated with parameters but with assumptions imposed by the modelling framework and can be evaluated through scenario analysis. In instances where model outcome uncertainty is substantial, it becomes crucial to determine whether additional research could reduce this uncertainty. The value of supplementary research can be assessed via Value of Information (VOI) analysis. As per Norwegian guidelines [40] on economic evaluations, the VOI must be calculated when a PSA has been done and there is decision uncertainty (when the probability that the new treatment is cost effective is less than 100%, but higher than 0%, for a range of common willingness to pay thresholds). VOI estimates the upper bound of the expected net health benefit that could potentially be gained per patient if the uncertainty surrounding their treatment choice could be resolved [44]. Furthermore, to ensure transparency and reproducibility in economic evaluations, it is essential to provide the model source code alongside the results.

Part II. Manuscript

Introduction

Lung cancer is the leading cause of death from cancer worldwide (18.4% of all cancer deaths), is the most commonly diagnosed cancer (11.6% of all cancers), and causes more deaths than breast, colorectal, and cervical cancers combined [1] and it covers the 19.79% of all malignant neoplasms related deaths in EU 27 (27 member states of EU) [2]. Smoking prevalence is decreasing in Western countries, however, 17 to 28% of adults currently still smoke, and smoking initiation remains substantial in youths [3]. Lung cancer and other tobacco related diseases are expected to remain important health problems worldwide for decades [4, 5]. The intervention under analysis is a risk-based lung cancer screening program. As a consequence of the fact that virtually no test is completely accurate, the benefits flowing from earlier identification and treatment of lung cancer must be offset by the likelihood that there will be some who may be falsely reassured by false-negative results and a number found to be false positives who will require further investigations and possibly experience additional anxiety relative to the situation in which no screening takes place [8].

The TIDL study, initiated in 2021, is an ongoing Norwegian pilot project conducted in Akershus County, primarily focusing on examining the impact of risk-based CT screening with annual screenings on the incidence of early-stage lung cancer. Additionally, the study aims to explore the feasibility of implementing a national lung cancer screening program [60, 61]. It was used to derive eligibility criteria for screening in our model.

Two large RCTs (the NLST in the United States and the Dutch–Belgian NELSON trial in Europe) have found that lung cancer screening with LDCT can reduce lung cancer by 20–24% in high-risk smokers [16, 17], and women may benefit more from screening than men [17, 18]. These studies can help shape the design of definitive large randomised trials [19–21], address knowledge gaps such as recruitment strategies to improve screening uptake [18, 22–26], how to reach lower socioeconomic groups and those who live in underserved areas to decrease disparity [26, 27], optimise screening selection criteria [25, 28, 29] (such as the PLCOm2012 tool, found to be easy to use and took around 5 min to administer, either using a form or electronically (web-based) [30] and the PLCO2012noRace model has been validated in a multiracial population in Chicago [31]), screening frequency and duration [29, 32, 33], nodule management [29], healthcare resource utilisation [29] and cost-effectiveness [24, 27, 29].

Lung cancer screening is most effective when applied to high-risk individuals [34, 35], as screening very low risk individuals has no lung cancer mortality reduction benefit. For example, in the NLST, individuals who had a 6-year lung cancer risk $< 0.64\%$ had non-significantly more lung cancer deaths in the LDCT group than the comparator group [36].

The objective of this is study is to establish whether a risk-based lung cancer screening program is cost-effective or not, in a Norwegian setting. Population-based organised screening programs for breast, cervical and colorectal cancers have been implemented around the world [30], but it is not the same for lung cancer.

Lung cancer screening in this specific setting represents an unmet knowledge gap, as no one has ever developed a microsimulation model for it, and cost-effectiveness analyses are required by Norwegian priority-setting criteria [40] to inform decisions.

A systematic review of cost-effectiveness analyses done by Snowsill [8] concluded that significant uncertainty remains as to the cost-effectiveness of LDCT screening for lung cancer. They have not produced consistent results in terms of the cost-effectiveness of screening, and certain factors regularly appeared as significant in determining cost-effectiveness: the cost of a LDCT scan, the risk of lung cancer (prevalence, and incidence for studies evaluating more than a single screen) in the screened cohort and the effectiveness of LDCT screening in broad terms (e.g. achieving a stage shift without significant over-diagnosis, extending lung cancer survival beyond lead time, reducing lung cancer mortality) [8]. Importantly, setting specific protocols and resource use are important to evaluate the cost-effectiveness across countries.

Methods

Analytic Overview

We developed a natural history microsimulation model of lung cancer, which is a type of decision-analytic model that allows the simulation of hypothetical individuals and scenarios (e.g., screening), and their health outcomes evaluation [45, 62]. Our model simulates 720 monthly cycles (60 years), in which every individual faces the risk of developing lung cancer, based on their age and risk-profile (smoking history). When an individual develops lung cancer, the tumour begins to grow according to a modified Gompertz function [55] for tumour growth (different by cell type, refer to *Disease Progression and Staging*). We used the output of the microsimulation model to evaluate the cost-effectiveness of different screening strategies, estimating the impact of different screening eligibility criteria.

This model and analysis focuses on the Norwegian high-risk population, including and distinguishing men and women, as a single cohort of $20,000$ individuals of 40-years-old over their remaining lifetime. Since the cohort represents a high-risk population, every individual has a smoking history (either as a smoker or an ex-smoker); non-smokers are excluded from the analysis. Please refer to Figure A1 for a schematic of the model.

In a primary analysis, our model compared a scenario with no screening, i.e., only the natural history of the disease, to a scenario with the screening policy strategy reflected by the Norwegian-pilot protocol for eligibility and screening management [60]. In a secondary analysis, we explored additional modification of eligibility criteria and different screening intervals. Model output included, both clinical (lung cancer incidence by age group, stage distribution, number of deaths due to lung cancer) health benefits (life-years (LY)s and QALYs), and economic outcomes (resources use and associated costs). Costs were expressed in 2023 Norwegian Krone (NOK).

Our results will be presented in two parts. Part one provides model-based projections of the clinical outcomes, while in part two, we estimate the cost-effectiveness of lung cancer screening.

We will use the ICER as a metric for cost-effectiveness, defined as the ratio of additional costs of one strategy compared with the next most costly strategy over incremental quality-adjusted life years of one strategy compared with the next most beneficial strategy. We included both medical direct and some indirect costs in our analysis, assuming an extended healthcare perspective and a discounting factor following the Norwegian guidelines [40]. We performed a one-way sensitivity analysis on the primary screening cost.

Natural History Model

Model Overview

Based on previous published lung cancer simulation model approaches [8, 63, 64], we developed a model that simulates the natural history of lung cancer in a series of 22 mutually exclusive, collectively exhaustive health states (starting from the healthy state, through undetected and detected lung cancer stages [65] and finally the death state). Each month, men and women can transition from no cancer (H) to early undiagnosed cancer (IA1_u) (informed by a Two-Stage Clonal Expansion (TSCE) model). Disease can progress to more severe stages of cancer where the probability of being symptomatically detected increases. With each increasing stage the probability of dying also increases. The entire model was developed in R [66], and the full source code is available to aid model transparency (See R Source Code), and our model is divided into two parts. The first part of the model simulates the natural history of lung cancer among the individuals, from a health state without lung cancer to death either due to lung cancer or other causes (refer to Natural History Model). The second part simulates the screening strategy. In the Screening Component, everyone eligible (see Table 4) will be screened. The benefit of screening is associated with favorable stage shift. More specifically, screening leads to diagnosis at earlier disease stage with better disease prognosis and more favorable life expectancy (refer to survival analysis *Mortality Analysis*). At the beginning it is assumed that individuals do not have nodal involvement and distant metastasis, and only over time they face a risk of developing both of them, every cycle. Based on the combination of tumour volume size, the extent of nodal involvement and/or the presence of distant metastasis tumours are classified into stages [65]. All tumour cases are assumed to be initially undiagnosed and that they can be detected in every cycle by symptom presentation. Our model included three possible lung cancer cell types: adenocarcinoma, small cell, and other, for the remaining cell types. In the natural history model, symptom detection is the only way to move from an undiagnosed stage to diagnosis; whereas in the screening component, eligible individuals can additionally be diagnosed through CT scans. Once a tumour is detected (either symptomatically or via screening), the stage of the tumour doesn't progress anymore and the mortality of the individual is derived from specific survival curves by stage (refer to Mortality Analysis). In addition to death from lung cancer, all the individuals could die from other causes in every cycle, and the risk differs among individuals according to their age, smoking history, and gender (refer to *Mortality Analysis* and to R Source Code).

Costs are assigned by stage and upon death, additional costs for screening were assigned in the screening scenario (refer to the Costs section for details). Utilities were assigned by health state in both scenarios, and we additionally included specific disutilities only related to the screening component (see details in Health-state related utilities section).

Two-Stage Clonal Expansion Model

Our model uses a TSCE [54] as a dose-response model, it is a well-known model already used by some major natural history models of lung cancer [67] in cost-effectiveness analyses, and it is implemented to derive hazard functions for the initiation of lung cancer. We use the TSCE model to

estimate the likelihood of developing a malignant tumour, which is the first possible transition from the healthy state in our model. Rather, a precancer state is not known for lung cancer and does not precede cancer development, excluding benign tumours. The TSCE model was applied separately to six different sub groups of individuals, to derive hazard functions (refer to Figure A2) that are specific to the risk-profile of the individuals (refer to Table A1). These sub-groups are mutually exclusive and based on the TIDL screening eligibility criteria [60], and they were used to get precise estimates of the hazard rates that were then dependent on both age and the smoking history of the individuals. The six profiles were designed to include all the individuals in the simulation. Profile 0 was assigned to everyone who was not specified in another profile, it is a baseline risk calculated on the entire sample of the NLST dataset (refer to *Epidemiological Input Parameters*). Profile 1 is defined to include only the smokers with a number of pack-years between 30 and 175. The remaining profiles focus on ex-smokers and the idea behind is to get different risks for ex-smokers with different times since smoking quit and number of pack-years. For instance, Profile 2 includes the most recent ex-smokers, those who quit in the last five years, and had a number of pack-years higher than 30. Profile 3,4,5 are made for those who quit before, so their time since smoking quit is between 5 and 10 years, and they are differentiated by their intensity of smoking. Profile 3 includes people with 30 to 50 pack-years, Profile 4 includes people with 50 to 75 pack-years and lastly Profile 5 includes people with more than 75 pack-years. In this way we can have different risk-profiles with specific hazard functions for smokers and ex-smokers. The TSCE reads individual data (refer to *Epidemiological Input Parameters*) and generates different hazard functions for smokers and ex-smokers, increasing by age, where the hazard rates of smokers were higher than the hazard rates of ex-smokers (refer to R Source Code). Non-smokers were not considered in this model. Consistently with previous analyses [68], we assumed a lag-time of five years to consider the time difference between the occurrence of a first malignant cell and the observation of cancer [54]. An example of individual data dataset read by the TSCE model can be found in Table A2.

Disease Progression and Staging

Disease progression is modelled through monthly probabilities of nodal involvement and presence of distant metastasis, conditioned on tumour size (T). Every tumour is initially undetected and assumed to be free of nodal involvement and distant metastasis. As the tumour grows in size (in diameter, it is assumed to be spherical) the chances of nodal involvement (N1, N2, N3) and distant metastasis (M1) change. There are four size intervals, based on the quartiles of the size distribution in the NLST dataset, and each size interval has different monthly probabilities to reflect that larger tumours have a higher chance of developing nodal involvement and/or distant metastasis, and they are not time dependent. The monthly probabilities of nodal and metastatic involvement by volume size were obtained via calibration (refer to *Epidemiological Input Parameters*), and they were then used as inputs in the final model. Calibration was performed manually initially to get a feeling of the upper and lower bounds of each probability (sixteen parameters in total, four probabilities for each of the four tumor size groups), and then it was automated through an optimization algorithm to find the best set of parameters (refer to calibration algorithm in the R Source Code and to Table A3 for the final calibrated parameters used in our model). The "NLOPT_LN_COBYLA" algorithm was used (COBYLA algorithm [69], from the *nloptr* package), for its simple implementation and speed. We built a smaller model was for the purpose of calibration and to speed up the calculation time, with an yearly cycle length instead of monthly, and then we converted back the obtained yearly probabilities to monthly probabilities.

The distributions of N and M in the NLST dataset by size at stage detection were used as calibration targets for the calculations (refer to R Source Code and to Table A4 for the NLST distributions used to calibrate our model).

Following the monthly update of TNMs (combination of their tumour size, extent of nodal involvement and presence of distant metastasis), a current cancer stage is mapped to a stage, based on the Eighth edition of TNM staging of lung cancer [65] (refer to Table A5).

After a stage is assigned, the tumour continues to grow and might involve lymph nodes, in that case the stage might vary and further progress. Every cycle the tumour faces the chance of being symptomatically detected (refer to *Epidemiological Input Parameters* for detection probabilities) and when it gets detected to a specific stage, the tumour won't progress anymore, and the individual will follow the stage-specific survival curve (refer to *Mortality Analysis*). Among those who are undetected, the tumour will then continue to grow and potentially progress until it will be eventually detected.

The growth function of the tumours, is described by a modified Gompertz function for tumour growth (see the Theory section for more details) [55], as follows:

$$y(t) = y_0 \left(\frac{K}{y_0}\right)^{\exp\left(-\exp\left(\frac{e\cdot\mu_{\max}\cdot(\lambda - t_G)}{\log\left(\frac{K}{y_0}\right)}+1\right)\right)}$$

where:

- $y(t)$ is the predicted size at time t.
- y_0 is the initial tumour size.
- K is the carrying capacity.
- $\mu_{\max}$ is the maximum tumour growth rate.
- λ is the lag time.
- t_G is the time at which growth is evaluated.
- e is the base of the natural logarithm.

The initial size, y_0, is the lowest possible size a tumour can have in our model, it is obtained from the minimum tumour size value from the NLST dataset. The carrying capacity, K, instead is the maximum size a tumour can have (refer to Table A6 for descriptive statistics of the tumour size in the NLST dataset). The growth rate parameters (refer to *Epidemiological Input Parameters* and see Table A7 for the actual values used in our model) vary according to the cell type of the tumour. Consistently with previous analyses [54, 68] we assumed a lag time, λ, of five years (refer to *TSCE*).

We distinguished the three types of lung cancer to better reflect the lung cancer cell type distribution of Norway [70], and to account for the different speed of growth of the cell types (adenocarcinoma is slower than the small cell histologic subtype [71]). At initiation, every individual is assigned to a histologic subtype according to their real-world distributions, and this is assumed to not change over time, and each individual can only one develop one tumour (refer to R Source Code).

Mortality Analysis

There are two possible causes of death in our model: death due to lung cancer and death due to other causes. Every individual faces a risk of dying from other causes in every cycle, which depends on age, gender, and smoking history. Other causes mortality rates were calculated subtracting the lung cancer specific mortality data from all causes mortality data. All causes mortality values are probabilities of death by age and gender [72] and lung cancer specific mortality values used here are the probabilities of dying from the disease by age and gender [73]. Lung cancer mortality specific hazard ratios [74] and all causes mortality hazard ratios [67], were multiplied by the original mortality values and used to estimate smoking status specific mortality rates (different mortality rates for smokers and ex-smokers) (refer to R Source Code for calculations).

When an individual is diagnosed with lung cancer the stage of the tumour doesn't progress anymore and the mortality of the individual is derived from specific survival curves by stage. Survival curves by stage are not specific to individuals' characteristics and were obtained using WebPlotDigitizer [75] (refer to *Disease Progression and Staging*).

The published graph of survival curves by stage [76] covered only five years after diagnosis, therefore we had to extrapolate using parametric survival assumptions [56] (refer to Figure A3 and to R Source Code). We predicted values using the Exponential, Weibull, Log-normal, and Log-logistic curves and then chose the curves leveraging visual inspection with the curve that fit the best according to the lowest AIC value. The survival function chosen for Stage I was the Exponential, the Weibull function was chosen for Stage II, and Log-normal for both Stage III and Stage IV (refer to Table A8).

Epidemiological Input Parameters

In order to get the initiation hazard functions from the TSCE model [54] we had to provide specific information (refer to Table A2 for an example of dataset and to Table A9 for descriptive statistics of the main input variables obtained from the NLST dataset), such as the age of the individual, the smoking onset and quitting age, average number of cigarettes smoked per day, number of pack-years smoked, the person years and whether it was a case of lung cancer or not. We obtained the individual patient-level data from the NLST study [77]. Individuals with the same characteristics were merged and their person-years were summed up. The TSCE model required information on whether the individuals had a confirmed lung cancer or not, and in Table A10 the proportion of confirmed lung cancer and confirmed non lung cancer cases from the NLST dataset is shown. The variable frequencies were determined from a subset of the original NLST dataset, which included people with a clear confirmation of lung cancer or a clear confirmation of not having lung cancer (people without a medical record or where this was pending or not reported were excluded), aged between sixty and seventy-nine years old (following the TIDL eligibility criteria).

The proportions of lung cancer cases with each different level of nodal involvement and the presence of distant metastasis at stage diagnosis, were our calibration targets, and they were obtained by NLST data (See Table A11). These distributions were obtained by quartiles of the volume size, at stage detection (see Table A4).

The tumour growth rate parameters were differentiated by cell type, to account for different growth speeds, and were obtained from the technical appendix of the Massachusetts General Hospital Institute for Technology Assessment (MGHITA) Microsimulation Model [71], and subsequently adapted to our monthly cycle length. The Norwegian lung cancer cell type distribution was obtained from a publicly available report [70]. The symptom detection probabilities by stage were obtained from the Snowsill [8] model, because they were derived from calculations on NLST data, our same source of individual level data.

Validation

The validation of our model is an essential element and plays a key-role in the interpretation of the results of this study. We performed cross validation by comparing our results to the cost-effectiveness analyses previously performed (see Results). We externally validated our natural history model outcomes to epidemiological data collected in Norway from the Nord-Trøndelag Health (HUNT) panel [78]; specifically, incidence by stage data, age-specific cancer incidence rates for a high-risk smoking population in Norway. However, the data in the HUNT panel was collected in the late 90's and early 2000's and did not contain a high enough number of heavy smokers [78].

Furthermore, we internally validated our natural history model by extreme value explorations, to make sure that our model was behaving correctly. We implemented input parameters from major models [71], and we used calibration techniques to fit real data and get monthly probabilities of nodal involvement and occurrence of distant metastasis.

Screening Component

In our analysis we included a base case scenario of screening according to the TIDL eligibility and management protocol compared with no screening. In addition, we conducted a secondary analysis that included five explorations of screening strategies, that varied the screening eligibility criteria and screening frequency (refer to Table 4). One of the key elements of the screening component is to identify the people who have the highest chances to benefit from screening, and we referred to the TIDL [60] and 4ITLR [43] inclusion criteria. We combined both eligibility criteria and to be qualified as eligible, an individual needed to be between 60 and 79 years old, currently smoke or have quit within the past decade, have smoked a minimum of 35 pack-years, and possess a PLCOm2012 score of at least 2.6% (following the 4ITLR [43] inclusion criteria). The PLCOm2012 (PLCOm2012) [79] score was calculated in the model for every individual alive and without a diagnosis of lung cancer. Table A12 and Table A13 show descriptive statistics of the main inputs of the PLCOm2012 score (refer to R Source Code for calculations, the official algorithm was adapted to account for age in months rather than years). The descriptive statistics are from the PLCOm2012 subset from the NLST dataset, which included information on the cancer history of the individuals and their family, the weight and height to calculate the Body Mass Index (BMI), the education level, ethnicity, age, and age at quit to calculate the number of years since smoking quit (Refer to R Source Code).

Detection

In our model with screening strategies, an individual could then be identified either through screening or from symptoms, or they may remain undetected and progress to more advanced stages of cancer. Importantly, screening will help to reduce the number of later detected stages and prevent the occurrence of distant metastasis (resulting in a lower proportion of stage IV cases). We assumed the screening compliance to be 100% to allow a comparison of the maximum benefit for each strategy, and we implemented screening test characteristics (i.e., sensitivity and specificity, obtained from the MGHITA model [71]) by volume size (refer to Table A14). In our model, it was then possible to incorrectly classify individuals as positive (false positive) despite not having the disease, or as negative (false negative) despite having the disease.

Screening Strategy

Once an individual was identified as eligible they were screened and the 4ITLR screening management protocol for CT Screen detected baseline scan non-calcified nodules was followed (refer to Figure A4), with a biennial screening interval in case of negative screen result. In the set of strategies we considered in our secondary analysis, we evaluated a different screening interval (period of time between multiple screens), minimum number of pack-years, and age restriction. Particularly, in the first scenario we extended the screening interval from 24 to 36 months; in the second scenario we increased the minimum number of pack-years smoked by the individual to be eligible for screening from 35 to 40, in the third scenario we increased it to 50 and in the fourth and last scenario we modified the upper age restriction cutting down the maximum age from 79 to 70.

Nodule Management

A positive screen occurred when the tumour vol-

ume size was 300mm^3 or higher, whereas a negative screen occurred when the tumour volume size was lower than 100mm^3, leaving the intermediate result for a volume size in between. In case of a positive results, the individual was diagnosed with lung cancer. In case of a negative result, the individual is considered safe and would be screened again after a specific screening interval (24 months in the base case scenario and then varied in scenario analyses). For individuals with an intermediate outcome, the strategy was to be monitored and receive another screen after three months. At the time of follow-up screen, the growth speed (Volume Doubling Time (VDT)) of the tumour would be considered as a risk indicator of malignancy. A VDT of 600 days or lower would lead to a positive screen result, and to a diagnosis of lung cancer, whereas a VDT of more than 600 days would lead to a negative screen result and the individual would then receive another screen after the specific screening interval (24 months in the base case scenario). The VDT is used as an indicator of significant change [8], and it was the NELSON [80] study that introduced a nodule volume analysis and a volume doubling time (as a biomarker for growth rate) methodology [43]. In the NELSON trial an exponential tumour growth function was assumed and the VDT calculation was pretty straightforward, according to the modified Schwartz formula [81]:

$$VDT = \frac{\Delta T \cdot \log 2}{\log\left(\frac{y_2}{y_1}\right)}$$

where:

- ΔT is the time interval between the two scans, indicating the change in time.
- y_1 and y_2 are the volumes of the nodule at the first and second scans, respectively.
- log refers to the natural logarithm.

In our model the calculations were different due to the different nature of the growth function, which depended on the specific growth rate that the tumour faces at that point in time, and since the growth rate is not constant it is not possible to use a fixed formula to calculate the VDT at every point in time. In order to get the VDT it was necessary to solve this equation for t_2:

$$2y_{(t_1)} = y_{(t_1)}\left(\frac{K}{y_{(t_1)}}\right)^{\exp\left(-\exp\left(\frac{e\cdot\mu_{\max}\cdot(\lambda-t_2)}{\log\left(\frac{K}{y_{(t_1)}}\right)}+1\right)\right)}$$

where:

- $2y_{(t_1)}$ is the predicted size at time t_2.
- $y_{(t_1)}$ is the initial tumour size at time t_1.
- K is the carrying capacity.
- $\mu_{\max}$ is the maximum tumour growth rate.
- λ is the lag time.
- t_2 is the time at which the volume is doubled.
- e is the base of the natural logarithm.

In R we used symbolic differentiation, which does not use numerical methods like Newton's method for its computations (computationally demanding), to derive the differential equation analytically and this function could then be numerically evaluated for all the future time steps (see R Source Code for specific calculations).

Cost and Effectiveness Data

Costs

The main direct medical costs of lung cancer were related to treatment (surgery, radiotherapy, systemic oncological treatment), diagnostic work-up (e.g., biopsy, positron emission tomography (PET) scan), and the cost of the screening. Furthermore, we included travel costs and a time cost of two hours, based on the Norwegian Medical Products Agency (NOMA) [82]. All cost inputs used in our model were derived from unpublished theses [61, 78], which employed calculations based on Norwegian recommendations and published data sources. In our model we assigned a lump sum cost by stage at detection for treatment costs (determined by the treatment options for patients reported by the Cancer Registry of Norway [70] and according to the Norwegian diagnosis-related group (DRG) weight [83]); a diagnostic workup cost that differs according to whether detection was due to symptom presentation or as a result of screening [83]; a cost for all the primary and follow-up screens [84], and a cost for false positive screen results [24]. Lastly, we assigned an end-of-life cost to those who faced lung cancer, that represents the incremental end-of-life cost due to the disease [85]. Dosing was taken from Norwegian guidelines [86] and no wastage was assumed in the calculations. All costs were adjusted for the official healthcare sector specific inflation to 2023 [87]. See Table A15 for the cost input values used in our model.

Health-state related utilities

In our model we first assigned a baseline background utility independently of the health state (apart death that was given no utility), according to the age and smoking profile [88–91]. We then

applied a reduction to the background value to account for a diagnosed stage of lung cancer (based on a multiplier obtained from calculations on published literature [92–94]), together with a monthly decrement of 0.063 for the diagnostic work-up [8], and implemented additional disutilities in case of a screening (both primary and follow-up screening, with a decrement of 0.010 for two consecutive months after the screening test [8]) and in case of a false positive test result (decrement of 0.063 for three consecutive months after the screening test [8]), when necessary. Special attention was given to respect the logical hierarchy of the utility values, applying a multiplicative approach to avoid the use of absolute utility values and cases where the utility of a diagnosed lung cancer stage is higher than the corresponding background value. See Table A15 for the utility input values used in our model.

Cost-effectiveness calculations

We calculated the ICERs by considering the strategies and their associated costs and effects, assigning them one of three statuses (non-dominated, extended dominated, or dominated), and calculates the incremental cost-effectiveness ratios for the non-dominated strategies. A non-dominated strategy is one for which no other strategy is both more effective and less costly. A dominated strategy exists if another strategy is both more effective and less costly. An extendedly dominated strategy, or extended dominance, occurs when a strategy is less cost-effective than a combination of other strategies and does not lie on the cost-effectiveness frontier [44].

Results

Validation. Our analysis of the clinical outcomes reveals an overestimation in the incidence of lung cancer by age group in our natural history model, which led our values to be generally on or just above the upper bound of the empirical data (see Table 1). This divergence from the expected incidence rates likely stems from an unidentified error in the TSCE model's implementation, which unfortunately remains undetermined at this stage of our research. However, our model successfully captured the shifts in lung cancer stage distributions (see Figure A5-A10) and the averted deaths from lung cancer (see Table A16), both attributable to the implementation of screening policies.

Clinical Outcomes. Compared with no screening, risk factor–based screening strategies were overall estimated to result in increased number of lung cancer deaths averted and higher *QALYs*, with variations according to the specific eligibility criteria for each scenario. In the base case screening scenario for example, we calculated a reduction of 7.0% in the number of deaths due to lung cancer compared to the no screening scenario (see Table A16 for the averted deaths percent reductions and absolute numbers). The model's ability to reflect the stage shifts and the reductions in mortality provides valuable understanding of the potential impact of lung cancer screening on health outcomes, including life expectancy and quality-adjusted life expectancy.

However, it is important to note that the overestimation of lung cancer incidence has a downstream effect on the mortality predictions. The model predicts a higher number of overall deaths from lung cancer, which is a direct consequence of the initially overestimated incidence rates.

Cost-Effectiveness Results. Our primary analysis showed that regardless of the health outcome measure (and both discounted and undiscounted) the risk factor–based screening base case policy (Table 4) would be considered cost-effective (Table 2) [95]. In our secondary analysis, when we competed five strategies with alternative eligibility criteria and screening intervals, we found that when using *QALYs* as health outcome, Scenario 4 (Table 4) would be the optimal choice, the base case screening scenario would still be cost-effective however with a higher *ICER*, Scenario 5 (Table 4) would not be cost-effective and the other options would be dominated (Table 3). When using life-years as health outcome (both discounted and undiscounted), the optimal choice would be the base case screening scenario, Scenario 5 would be cost-effective and the other options would be dominated (Table 3). Due to the computational intensive calculations of our model we carried out a one-way sensitivity analysis on the primary screening cost, and the analysis showed a positive relationship between the primary screen cost and the ICER (Table 5).

Discussion

Findings. In our analysis we evaluated the cost-effectiveness of a lung cancer screening policy in the high risk Norwegian population according to different specific eligibility criteria. For this purpose, we developed a comprehensive decision analytic microsimulation model that simulates the natural history of the disease to estimate the expected impact of the interventions considered, and we performed different scenario analyses to explore the range of options. Risk-based lung screening programs are expected to be cost-effective compared with the current absence of screening program.

Comparison with previous literature. When comparing our estimate with other cost-effectiveness analyses from the published literature we find somehow similar results, even if with a lot of variance: it might be cost-effective at a threshold of £30,000 per QALY [8], between 27,756 USD and 243,077

USD per QALY according to a 2016 systematic literature review [96], 3,297 EUR per QALY in the Italian setting [97] (34,348 NOK 2022 [98]), 6,718 EUR per QALY (69,987 NOK 2022 [98]) [99] in Hungary, from 24,972 to 48,369 EUR (261,582 to 506,665 NOK 2022 [98]) per QALY [100] in Switzerland, range of 49,200 to 96,700 USD [101] (491,154 to 965,337 NOK 2022 [98]) and even higher than 100,000 USD [102, 103], both in the US.

Assumptions and limitations

Our results, however, should be interpreted carefully under the light of our model's limitations. At this stage of our research, the main shortfall of our model is its inability to accurately reflect the clinical outcomes of lung cancer, overestimating the incidence and the number of deaths, which has a boosting effect on the cost-effectiveness of the screening policy. It is reasonable to believe that a more accurate estimation of the clinical outcomes would lead to a less cost-effective result. We also noted a somehow low number of averted deaths and Stages IV in our model.

Smoking History and Hazard Function Estimation. In the estimation of lung cancer initiation hazard function, we only consider the smoking history, status of smoker or former smoker, and age of the individuals, but we are not able to reflect their smoking intensity and we do not distinguish the hazard functions by gender.

Tumour Growth Modelling. We modelled the growth of lung cancer differently by histologic cell type, however the growth function implemented does not currently vary by smoking status, a faster growth could be allowed for smokers and vice versa for ex-smokers, and does not differ between genders. We assume the tumour volume to be spherical, to track only one diameter and setting a minimum and maximum value for the tumour size, based on NLST values, and we obtained the growth rate parameters by cell type from published literature [71]. However, the ideal setting would be to have data on the tumour volume size over time, to track the growth development and fit a Gompertz function on real data, unfortunately those data were not available.

Exclusion of Benign Tumors and Multiple Tumors. We did not include benign tumours (nodule size and growth are the most important predictors of malignancy [104] but in our model they are all considered malignant), multiple tumours per person and different possible locations of the tumours. Usually, only cancers that are likely to reduce life expectancy should be treated, whereas individuals with benign disease should return to the screening strategy [105], but since in our case there is no distinction, all the diagnosed cancers were treated as malignant.

Smoking Relapse and Behavioral Changes. We do not account for smoking relapse, meaning that there is no probability that an ex-smoker starts smoking again, and also there is no dynamism in the other direction, we do not allow smokers to quit over time. Every individual keeps the same smoking status during the entire simulation, we do not consider behavioural changes.

Disease Progression and Calibration. We modelled disease progression through monthly probabilities of involvement of lymph nodes and development of distant metastases, in an ad hoc smaller model developed for calibration, and we assumed that all the individuals initially started without any involvement and distant metastasis. However, to save computational time, we converted the cycle length to years and then reconverted the calibrated probabilities back to the monthly scale. This might have led to a less accurate calibration of our parameters, possibly explaining the small proportion of Stage IV cases.

Survival Hazard Functions. We modelled survival hazard functions as piece-wise-constant hazard functions, meaning that the hazard rate was assumed to be constant within specified intervals of time (the monthly cycle length) but varied between different intervals. Lung cancer survival curves were applied only by stage and considered the time since diagnosis, they were not obtained by treatment, age of the individuals at that time, or gender. Other causes mortality rates, on the other hand, were calculated by gender.

Detection and Screening Policies. We assumed that undetected cases of lung cancer do not lead to death from lung cancer, as it is believed that they would probably be diagnosed first, either via symptoms presentation or screening [8]. The detection probabilities that we implemented were given by stage, and do not vary by cell type and over time. For the screening policy we assumed an adherence of 1 to screening, to evaluate the maximum possible benefit for each strategy. However, it would be possible in future research to vary the adherence to explore multiple scenarios.

Screening Bias and Mortality Benefits. In the screening scenarios, when an individual was detected at an earlier stage than in the natural history model, their survival would be prolonged because they would then follow survival curves from the new stage. On the other hand, if an individual was diagnosed by screening at the same stage as they would have been diagnosed by symptoms presentation in the natural history model, their survival might be shortened. This is the lead-time screening bias, and at this stage of our research it was not addressed in

our model. Possible solutions would be to explicitly set that death in the screening arm cannot occur before death in the natural history model simulation. Furthermore, in our model the benefits of screening are only reflected on lung cancer mortality, not taking into account screening-associated non-lung cancer mortality benefits [106] and other incidental findings [107].

Cost-Effectiveness Analysis. As far as concerns the cost-effectiveness analysis itself, we assigned individuals to receive care consistently with the treatment guidelines and we did not allow for any variation. We assigned costs of treatment and diagnostic workup to individuals who got diagnosed by lung cancer, but we did not estimate a cost associated with survival of lung cancer in the first months, to distinguish people who died sooner or later than the others. Background health-state related utilities of individuals do not differ by gender, but they account for the smoking status and the intensity of smoking. Undetected cases of lung cancer were not assigned with disutilities, because when the disease is not diagnosed there is a lot of uncertainty and subjectivity around the burden itself, as it can largely vary among individuals. Finally, due to the complex nature of our microsimulation model, we were not able to perform any PSA and VOI analysis on our results. These analyses would have incorporated joint uncertainty and quantified the level of uncertainty in the preferred strategy, as well as determined the value of conducting additional studies to reduce uncertainty.

Conclusion

Our objective was to provide quantitative insight to policy makers about the cost-effectiveness of risk-based lung cancer screening policies in Norway. In our primary analysis we conclude that a risk-based lung screening program is expected to be cost-effective compared with the current absence of screening program. In our secondary analysis we discovered that Scenario 4 (same as base case scenario but with a reduced age range criterion for eligibility, include people only up to 70 years old instead of 79) would be the preferred cost-effective strategy. Further research is needed to correctly implement the TSCE model and refine the model's accuracy. This will enhance our understanding of lung cancer progression and the impact of screening policies, ultimately leading to more effective public health interventions in Norway.

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Tables and Figures

Table 1: Lung Cancer Incidence By Age Group

	Incidence Rate	Incidence Rate Among Eligible	HUNT – Incidence [CI 95%]
40-44	34.001	0	0
45-49	126.014	92.966	0
50-54	167.104	98.953	0
55-59	200.266	217.727	0
60-64	235.660	238.668	77.64[26.39, 128.89]
65-69	272.154	272.154	168.055[84.32, 251.79]
70-74	292.966	292.966	150.005[51.06, 248.95]
75-79	319.934	320.241	228.25[68.81, 387.69]
80-84	346.220	0	199.435[0, 417.03]
85-89	336.119	0	0
90-94	377.958	0	0
95-99	369.984	0	0

Note: The first column of the table shows the incidence of diagnosed lung cancer by age group in the Natural History Model (NHM). The second column shows the incidence only among screening eligible people in the same No Screening simulation. The last column shows the incidence by age group from the Nord-Trøndelag Health (HUNT) study [78, 108]. Please refer to the Discussion Component for details.

Table 2: Cost-Effectiveness Results Primary Analysis

QALY	Strategy	Cost	Effect	Incremental Cost	Incremental Effect	ICER (NOK/QALY)
Discounted						
	No Screening	13,094	213.016	NA	NA	NA
	Screening - Base Case	24,783	213.106	11,689	0.090	129,689
Undiscounted						
	No Screning	47,934	541.909	NA	NA	NA
	Screening - Base Case	76,825	542.693	28,891	0.784	36,868
Life-Years (LY)	**Strategy**	**Cost**	**Effect**	**Incremental Cost**	**Incremental Effect**	**ICER (NOK/LY)**
Discounted						
	No Screening	13,094	271.740	NA	NA	NA
	Screening - Base Case	24,783	271.874	11,689	0.134	87,045
Undiscounted						
	No Screening	47,934	713.630	NA	NA	NA
	Screening - Base Case	76,825	714.436	28,891	0.806	35,845

Note: This table presents our Cost-Effectiveness (CE) results from the prmimary analysis and shows the Incremental Cost-Effectiveness Ratios (ICERs) by outcome measure (Quality-adjusted life year (QALY) and Life Year (LY)) and discounting factor (Discounted and Undiscounted). The primary analysis shows positive health effects in the Screening scenario, regardless of the chosen health outcome. Refer to the Results section for the interpretation.

Table 3: Cost-Effectiveness Results Secondary Analysis

QALY	Strategy	Cost	Effect	Incremental Cost	Incremental Effect	ICER (NOK/QALY)	Status
Discounted							
	No Screening	13,094	213.016	NA	NA	NA	ND
	Screening - Scenario 4	21,730	213.091	8,636	0.075	115,431	ND
	Screening - Base Case	24,783	213.106	3,053	0.015	199,330	ND
	Screening - Scenario 5	43,397	213.124	18,614	0.018	1,013	ND
	Screening - Scenario 2	24,601	213.097	NA	NA	NA	ED
	Screening - Scenario 1	21,576	213.006	NA	NA	NA	D
	Screening - Scenario 3	23,925	213.042	NA	NA	NA	D
Undiscounted							
	No Screening	47,934	541.909	NA	NA	NA	ND
	Screening - Scenario 4	65,997	542.496	18,062	0.587	30,796	ND
	Screening - Base Case	76,825	542.693	10,829	0.197	54,934	ND
	Screening - Scenario 5	126,534	542.866	49,708	0.173	286,693	ND
	Screening - Scenario 2	76,271	542.677	NA	NA	NA	ED
	Screening - Scenario 1	68,130	542.234	NA	NA	NA	D
	Screening - Scenario 3	74,062	542.450	NA	NA	NA	D

Life-Years (LY)	Strategy	Cost	Effect	Incremental Cost	Incremental Effect	ICER (NOK/LY)	Status
Discounted							
	No Screening	13,093.880	271.740	NA	NA	NA	ND
	Screening - Base Case	24,783.030	271.874	11,689	0.134	87,045	ND
	Screening - Scenario 5	43,396.800	271.963	18,614	0.089	209,526	ND
	Screening - Scenario 4	21,729.960	271.837	NA	NA	NA	ED
	Screening - Scenario 2	24,601.290	271.858	NA	NA	NA	ED
	Screening - Scenario 1	21,576.140	271.709	NA	NA	NA	D
	Screening - Scenario 3	23,925.130	271.778	NA	NA	NA	D
Undiscounted							
	No Screening	13,093.880	713.630	NA	NA	NA	ND
	Screening - Base Case	24,783.030	714.436	11,689	0.806	14,508	ND
	Screening - Scenario 5	43,396.800	714.791	18,614	0.355	52,433	ND
	Screening - Scenario 1	21,576.140	713.742	NA	NA	NA	ED
	Screening - Scenario 4	21,729.960	714.148	NA	NA	NA	ED
	Screening - Scenario 2	24,601.290	714.385	NA	NA	NA	ED
	Screening - Scenario 3	23,925.130	714.056	NA	NA	NA	D

Note: This table presents our Cost-Effectiveness (CE) results from the secondary analysis and shows the Incremental Cost-Effectiveness Ratios (ICERs) by outcome measure (Quality-adjusted life year (QALY) and Life Year (LY)) and discounting factor (Discounted and Undiscounted). Please refer to Table 4 for the different scenario descriptions and to the Results section for the interpretation.

Table 4: Eligibility Criteria and different Scenario Analyses

	Base Case Scenario	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Number of pack-years	35	35	**40**	**50**	35	35
Smoking history	Smoker or quit time <10 years	Smoker or quit time <10 years	Smoker or quit time <10 years	Smoker or quit time <10 years	Smoker or quit time <10 years	Smoker or quit time <10 years
Age	60-79	60-79	60-79	60-79	**60-70**	60-79
PLCOm2012 score	2.6%	2.6%	2.6%	2.6%	2.6%	2.6%
Screening interval	24 months	**36 months**	24 months	24 months	24 months	**12 months**
Follow-up interval	3 months	3 months	3 months	3 months	3 months	3 months
Primary Screen Cost	3280.031 NOK	3280.031 NOK	3280.031 NOK	3280.031 NOK	3280.031 NOK	3280.031 NOK

Note: This table presents the eligibility criteria in the different scenarios, the screening intervals, and the total cost associated with the primary screen cost. The base case scenario reflects the Tidlig diagnostikk av lungekreft (TIDL) [60] and 4-IN-THE-LUNG-RUN (4ITLR) [43] inclusion criteria. In Scenario 1 we changed the screening interval from 24 to 26 months, in Scenario 2 and 3 we increased the minimum number of pack-years smoked from 35 to 40 and 50 respectively. In Scenario 4 we reduced the age range to include people only up to 70 years old, and in Scenario 5 we tested an annual screening interval, from 24 to 12 months.

Table 5: Cost-Effectiveness Results Sensitivity Analysis

QALY	Strategy	Primary Screen Cost Multiplier	Cost	Effect	Incremental Cost	Incremental Effect	ICER (NOK/QALY)
Discounted							
	No Screening	1	13,094	213.016	NA	NA	NA
	Screening - Sensitivity 1	0.25	18,785	213.106	5,691	0.090	63,145
	Screening - Sensitivity 2	0.5	21,784	213.106	8,690	0.090	96,417
	Screening - Base Case	1	24,783	213.106	11,689	0.090	129,689
	Screening - Sensitivity 3	1.5	27,782	213.106	14,688	0.090	162,961
	Screening - Sensitivity 4	1.75	30,781	213.106	17,687	0.090	196,233
Undiscounted							
	No Screening	1	47,934	541.909	NA	NA	NA
	Screening - Sensitivity 1	0.25	59,819	542.693	11,885	0.784	15,166
	Screening - Sensitivity 2	0.5	68,322	542.693	20,388	0.784	26,017
	Screening - Base Case	1	76,825	542.693	28,891	0.784	36,866
	Screening - Sensitivity	1.5 3	85,328	542.693	37,394	0.784	47,718
	Screening - Sensitivity 4	1.75	93,832	542.693	45,897	0.784	58,569
Life-Years (LY)	Strategy	Primary Screen Cost Multiplier	Cost	Effect	Incremental Cost	Incremental Effect	ICER (NOK/LY)
Discounted							
	No Screening	1	13,094	271.740	NA	NA	NA
	Screening - Sensitivity 1	0.25	18,785	271.874	5,691	0.134	42,382
	Screening - Sensitivity 2	0.5	21,784	271.874	8,690	0.134	64,714
	Screening - Base Case	1	24,783	271.874	11,689	0.134	87,045
	Screening - Sensitivity 3	1.5	27,782	271.874	14,688	0.134	109,377
	Screening - Sensitivity 4	1.75	30,781	271.874	17,687	0.134	131,709
Undiscounted							
	No Screening	1	13,094	713.630	NA	NA	NA
	Screening - Sensitivity 1	0.25	18,785	714.436	5,691	0.806	7,064
	Screening - Sensitivity 2	0.5	21,784	714.436	8,690	0.806	10,786
	Screening - Base Case	1	24,783	714.436	11,689	0.806	14,508
	Screening - Sensitivity 3	1.5	27,782	714.436	14,688	0.806	18,230
	Screening - Sensitivity 4	1.75	30,781	714.436	17,687	0.806	21,952

Note: This table presents our Cost-Effectiveness (CE) results from the sensitivity analysis around the cost of primary screening (Primary Screen Cost Multiplier) and shows the Incremental Cost-Effectiveness Ratios (ICERs) by outcome measure (Quality-adjusted life year (QALY) and Life Year (LY)) and discounting factor (Discounted and Undiscounted). Please refer to the Results section for the interpretation.

Appendices

Appendix I - Source Code

The entire source code is available from GitHub, Inc (`https://github.com/jacopo-disilvestre/LCMicrosim`)

Appendix II - Other relevant figures and tables

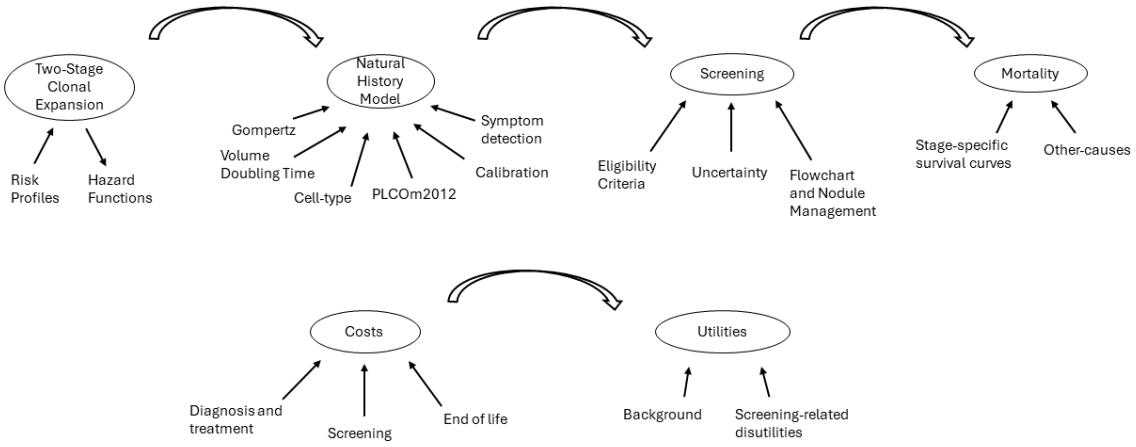

Figure A1: Schematic of the model

Note: This figure shows the model's schematic. The first step is to derive hazard functions from the Two-Stage Clonal Expansion Model, according to different specific risk-profiles. Once that lung cancer initiation is derived, the tumour begins to grow, and together with monthly calibrated probabilities of nodal involvement and development of distant metastases, the tumour progresses through different stages. The third phase is the screening strategy, according to the specific eligibility criteria and the detected nodules management strategy; screening accounts for uncertainty around the screen outcomes, accounting for false positives and negatives. The fourth step is a mortality analysis, derived according to stage-specific survival curves and other-causes mortality probabilities. Finally, costs and utilities are assigned to all individuals according to their characteristics, stage, disease, screening, and smoking history.

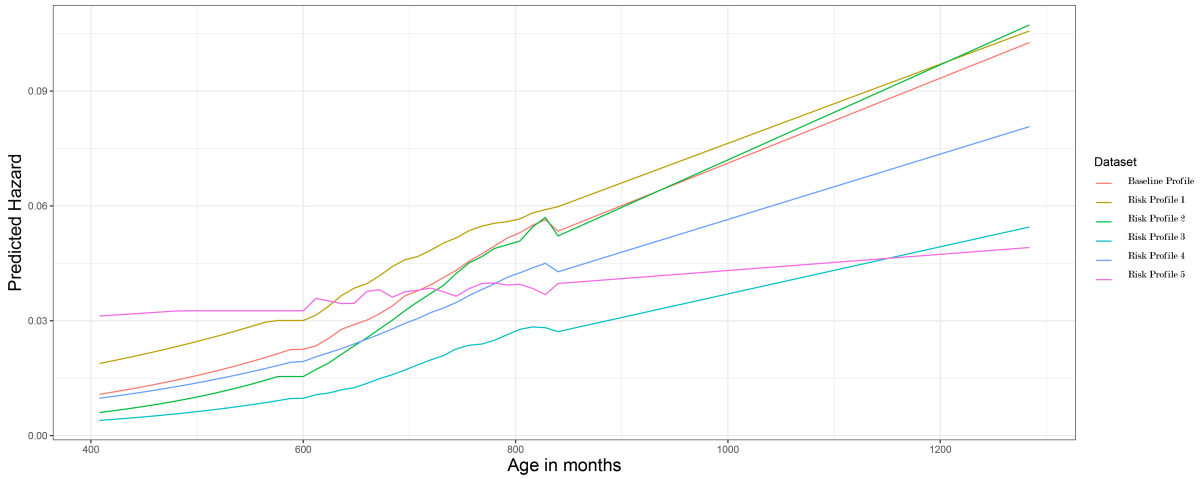

Figure A2: Predicted Lung Cancer Conversion Hazard by Risk-Profile

Note: the graph shows the predicted initiation hazard functions for the different risk-profiles described in Table A1, obtained from the Two-Stage Clonal Expansion model.

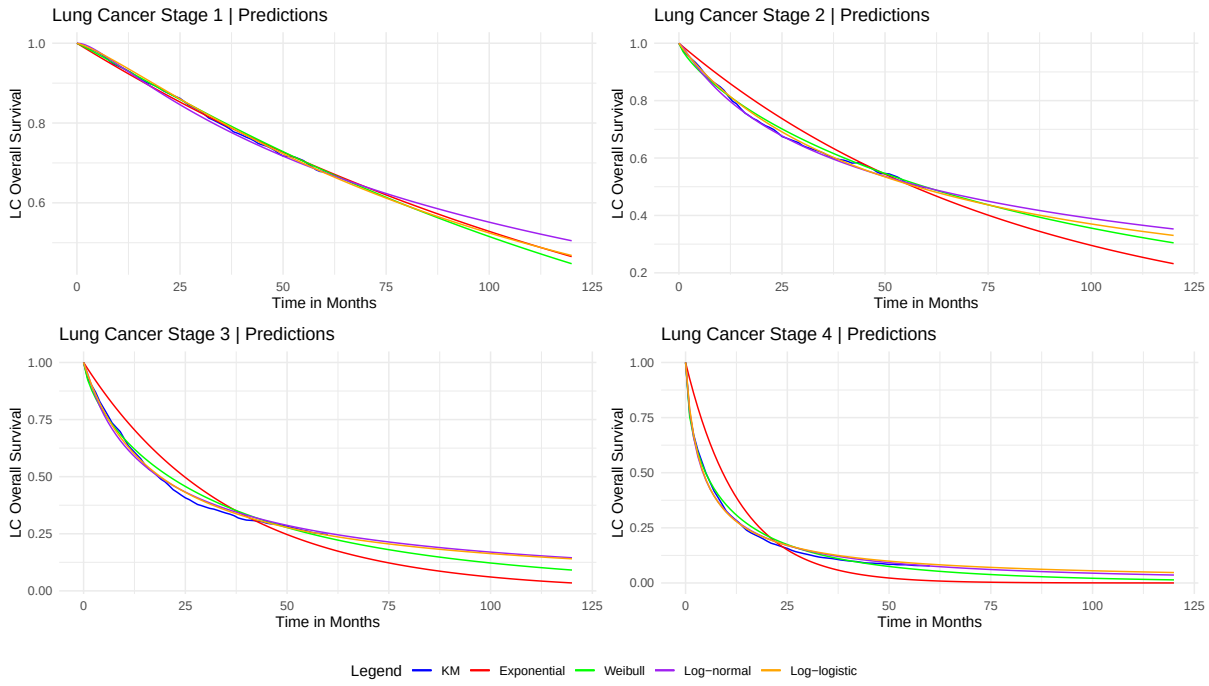

Figure A3: Survival Curves by stage of lung cancer

Note: each graph shows the different possible predicted stage specific survival curves based on Norwegian data [76] and obtained by a survival analysis, See Mortality Analysis

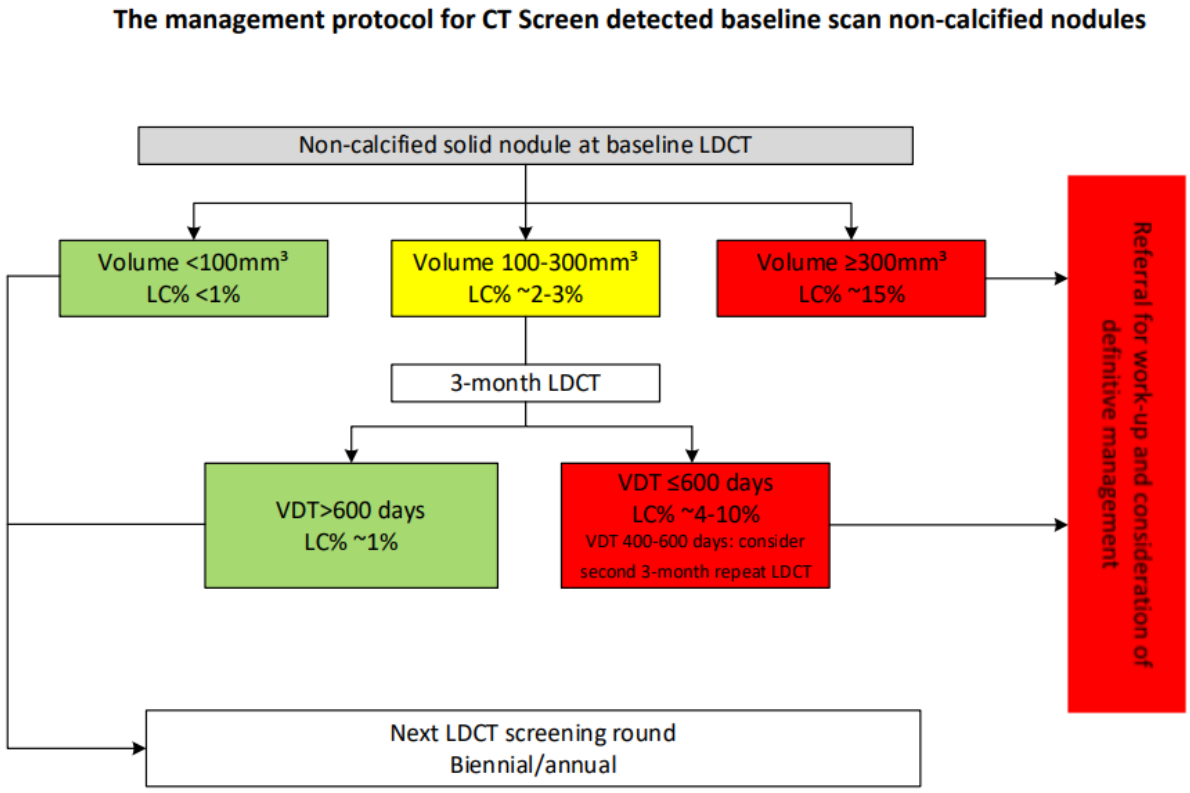

Figure A4: Screening flowchart in our model

Note: The picture shows the screening flowchart from 4-IN-THE-LUNG-RUN (4ITLR) trial [43] that we adopted in our model. Refer to the Screening Component for further details.

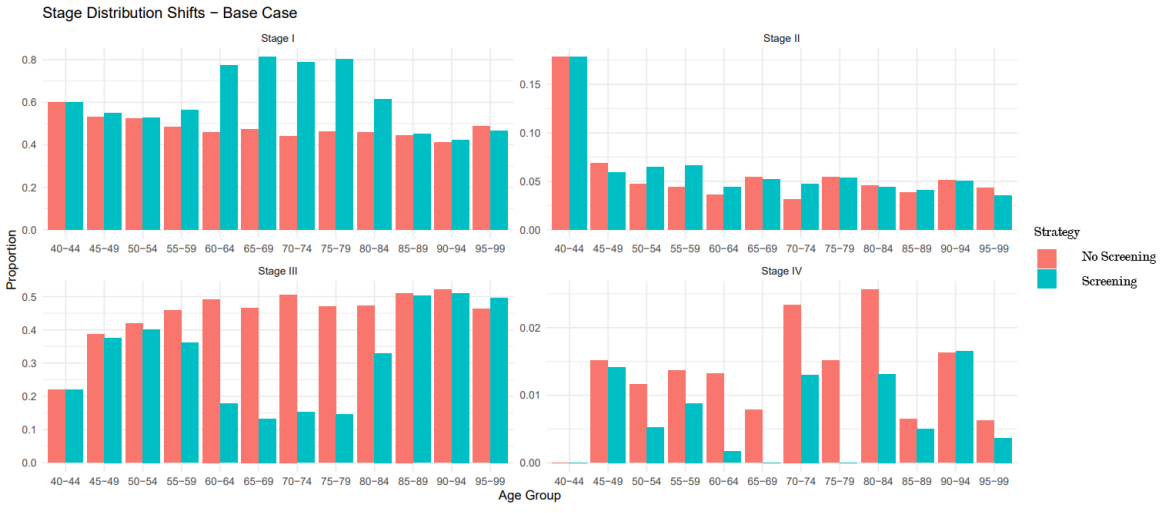

Figure A5: Stage Shifts in the Base Case scenario

Note: The picture shows the stage distribution shifts between No Screening and the Base Case Screening scenario. The effect of screening can be seen by the shifts towards lower stages of the disease from higher stages, mostly around the individuals whom age classified them as eligible and especially from Stage III and IV (red bars are higher than the green ones) towards Stage I (green bars are higher than the red ones). Please refer to the Screening and Discussion Components for further details. Please note the different y-axes, to highlight the difference in proportions.

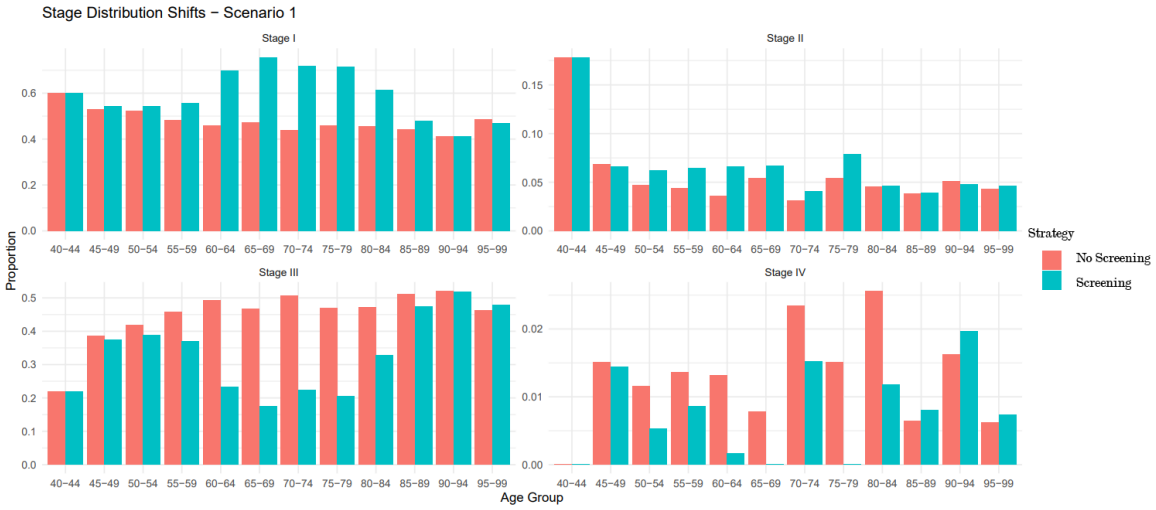

Figure A6: Stage Shifts in Scenario 1

Note: The picture shows the stage distribution shifts between the No Screening and the First Screening scenario variation. The effect of screening can be seen by the shifts towards lower stages of the disease from higher stages, mostly around the individuals whom age classified them as eligible and especially from Stage III and IV (red bars are higher than the green ones) towards Stage I (green bars are higher than the red ones). Please refer to the Screening and Discussion Components for further details. Please note the different y-axes, to highlight the difference in proportions.

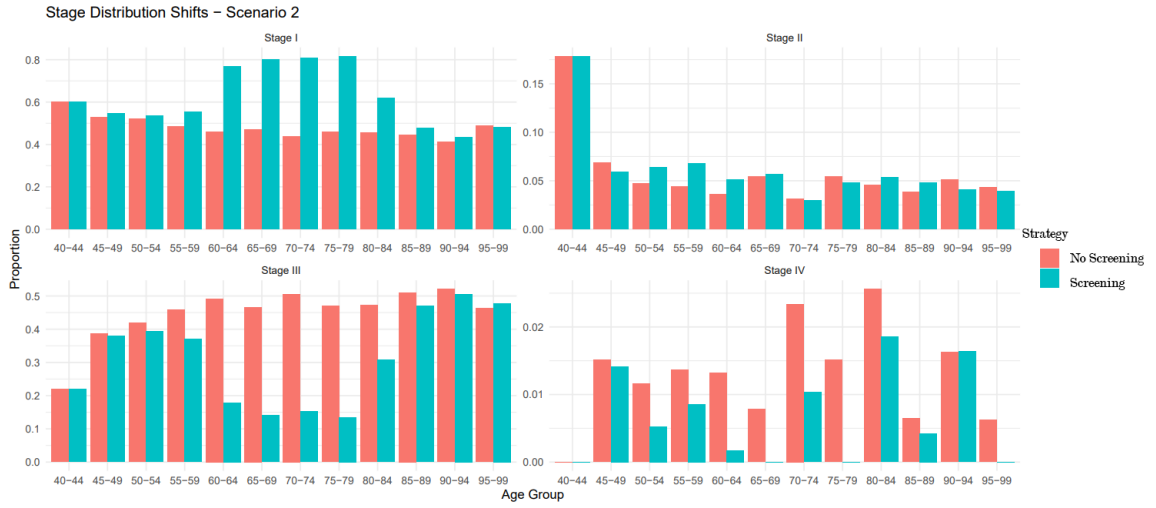

Figure A7: Stage Shifts in Scenario 2

Note: The picture shows the stage distribution shifts between No Screening and the Second Screening scenario variation. The effect of screening can be seen by the shifts towards lower stages of the disease from higher stages, mostly around the individuals whom age classified them as eligible and especially from Stage III and IV (red bars are higher than the green ones) towards Stage I (green bars are higher than the red ones). Please refer to the Screening and Discussion Components for further details. Please note the different y-axes, to highlight the difference in proportions.

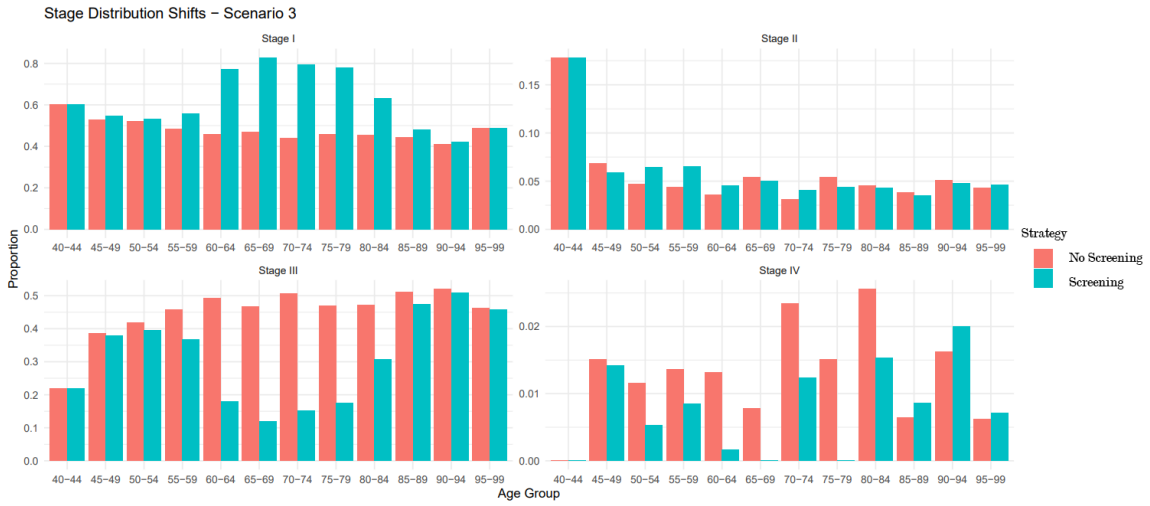

Figure A8: Stage Shifts in Scenario 3

Note: The picture shows the stage distribution shifts between No Screening and the Third Screening scenario variation. The effect of screening can be seen by the shifts towards lower stages of the disease from higher stages, mostly around the individuals whom age classified them as eligible and especially from Stage III and IV (red bars are higher than the green ones) towards Stage I (green bars are higher than the red ones). Please refer to the Screening and Discussion Components for further details. Please note the different y-axes, to highlight the difference in proportions.

Figure A9: Stage Shifts in Scenario 4

Note: The picture shows the stage distribution shifts between No Screening and the Fourth Screening scenario variation. The effect of screening can be seen by the shifts towards lower stages of the disease from higher stages, mostly around the individuals whom age classified them as eligible and especially from Stage III and IV (red bars are higher than the green ones) towards Stage I (green bars are higher than the red ones). Please refer to the Screening and Discussion Components for further details. Please note the different y-axes, to highlight the difference in proportions.

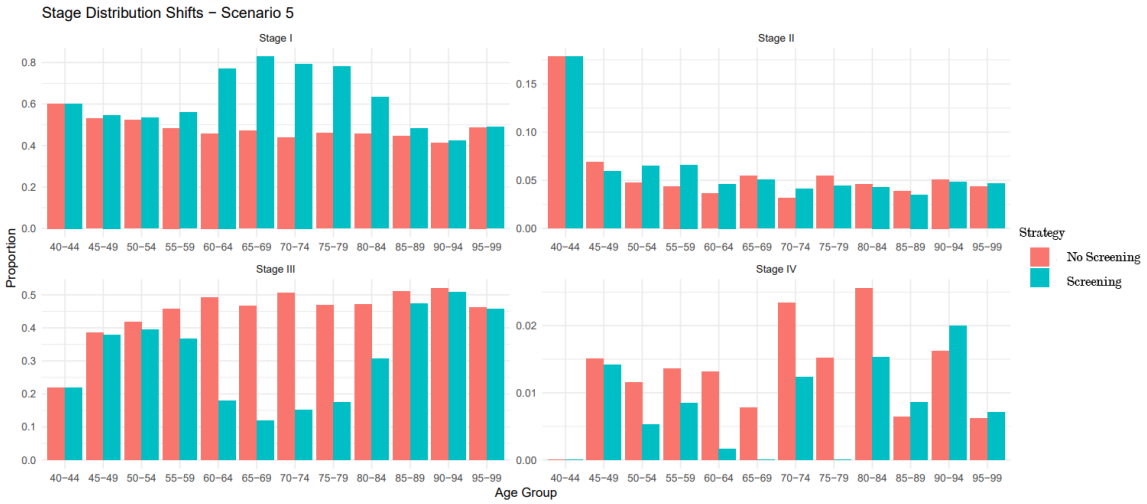

Figure A10: Stage Shifts in Scenario 5

Note: The picture shows the stage distribution shifts between No Screening and the Fifth Screening scenario variation. The effect of screening can be seen by the shifts towards lower stages of the disease from higher stages, mostly around the individuals whom age classified them as eligible and especially from Stage III and IV (red bars are higher than the green ones) towards Stage I (green bars are higher than the red ones). Please refer to the Screening and Discussion Components for further details. Please note the different y-axes, to highlight the difference in proportions.

Table A1: Different risk profiles read by the Two-Stage Clonal Expansion model

	Smoking Status	Smoking Quit Time (SQT)	Pack-years (pkyr)
Baseline Profile	everyone	everyone	everyone
Profile 1	1	0	30 <= pkyr <175
Profile 2	0	0 <SQT <= 5	pkyr >= 30
Profile 3	0	5 <SQT <= 10	30 <= pkyr <50
Profile 4	0	5 <SQT <= 10	50 <= pkyr <75
Profile 5	0	5 <SQT <= 10	pkyr >= 75

Note: Smoking status (1 smokers, 0 former smokers), Time since smoking quit in years, Total number of pack-years smoked. The table shows the different risk-profiles used in the Two-Stage Clonal Expansion model.

Table A2: Hypothetical lung cancer data set for *Two-Stage Clonal Expansion (TSCE)* calculations

age	ageStart	ageQuit	cigsPerDay	pyr	cases	laggedAge
65	10	65	11	6.998	0	60
71	16	71	11	4.674	1	66
64	13	64	12	6.303	0	59
68	15	68	12	3.795	0	63
70	18	70	12	6.992	0	65
71	18	71	12	6.396	0	66
74	15	74	12	6.215	1	69
74	22	74	12	6.283	0	69
65	14	65	13	7.025	0	60
68	10	68	13	7.264	0	63

Note: Actual age at the time of survey, Age at smoking onset, Age at smoking quit, Number of cigarettes per day, Total number of person-years (follow-up time), Total number of lung cancer cases, Lagged age. The table shows an example of dataset read by the TSCE model. Refer to TSCE for details

Table A3: Final calibrated probabilities of nodal involvement and distant metastasis, by tumour size quartiles

	P(N1|N0)	P(N2|N1)	P(N3|N2)	P(M1|M0)
(0,15]	0.027	0.099	0.058	0.008
(15,25]	0.056	0.193	0.096	0.007
(25,40]	0.062	0.265	0.083	0.016
(40,260]	0.092	0.290	0.165	0.076

Note: Columns: Probability of nodal involvement N1 given the initial absence of nodal involvement N0. Probability of nodal involvement N2 given the initial nodal involvement N1. Probability of nodal involvement N3 given the initial nodal involvement N2. Probability of distant metastasis M1 given the initial absence of distant metastasis M0. Rows: Tumour size quartiles in millimeters. The table shows the probabilities of getting nodal involvement and distant metastasis by volume size, used in Disease Progression and Staging.

Table A4: Calibration Targets

	N0	N1	N2	N3		M0	M1	
(0,15]	0.804	0.026	0.120	0.050	1	0.990	0.010	1
(15,25]	0.686	0.068	0.176	0.070	1	0.982	0.018	1
(25,40]	0.490	0.099	0.312	0.099	1	0.971	0.029	1
(40,260]	0.321	0.080	0.440	0.159	1	0.951	0.049	1

Note: Columns: Extent of nodal involvement and presence of distant metastasis. Rows: Tumour size quartiles in millimeters. The table shows the distributions of nodal involvement and distant metastases by tumour size at stage detection in the Two-Stage Clonal Expansion dataset, and they were used as calibration targets to get the corresponding monthly probabilities. Refer to Disease Progression and Staging

Table A5: Simplified Eighth Edition Lung Cancer Stage Classification

	N0	N1	N2	N3
T1A	IA1	IIB	IIIA	IIIB
T1B	IA2	IIB	IIIA	IIIB
T1C	IA3	IIB	IIIA	IIIB
T2A	IB	IIB	IIIA	IIIB
T2B	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1	IVA	IVA	IVA	IVA

Note: Columns: Extent of lymph nodes involvement (N0,N1,N2,N3)
Rows: Increasing tumour size (T1A, T1B, T1C, T2A, T2B, T3, T4) and presence of distant metastasis (M1). The table shows the stage classification used in our model. Refer to Disease Progression and Staging for details.

Table A6: Descriptive Statistics the tumour size in the *National Lung Screening Trial (NLST)* Dataset

	lesionsize
n	1,698
mean	31.277
sd	22.146
median	25
trimmed	27.940
mad	16.309
min	1
max	260
range	259
skew	1.983
kurtosis	8.510
se	0.537

Note: Lesion size of the tumour in millimeters. The table shows descriptive statistics of the tumour size variable in the NLST dataset, used in Disease Progression and Staging.

Table A7: Growth rate parameters used in the Gompertz growth function, by cell type

Cell Type	Distribution of growth parameter
Adenocarcinoma	$rlnorm(\text{meanlog} = -7.765, \text{sdlog} = 0.5504)$
Small cell	$rlnorm(\text{meanlog} = -5.44357, \text{sdlog} = 0.611485)$
Other	$rlnorm(\text{meanlog} = -6.6111, \text{sdlog} = 0.7935)$

Note: The growth rate parameters by cell type are calculated using a log-normal distribution with specific mean and standard deviation parameters (meanlog and sdlog, respectively). They were then adjusted for the number of cycles to normalize the growth rates.

Table A8: *Akaike Information Criterion (AIC)* values calculated in the survival analysis

	Exponential	Weibull	Log-normal	Log-logistic
Stage I	**2932.66**	2933.71	2941.90	2939.30
Stage II	1418.87	**1409.99**	1412.61	1412.92
Stage III	3772.67	3707.07	**3705.77**	3698.37
Stage IV	7123.60	6599.24	**6585.95**	6586.80

Note: The table shows AIC values for each survival function by stage. Refer to Mortality Analysis.

Table A9: Descriptive Statistics of the main variables used in *Two-Stage Clonal Expansion (TSCE)* calculations

	age	ageStart	ageQuit	cigsPerDay	pyr	laggedAge
n	2,793	2,793	2,793	2,793	2,793	2,793
mean	65.804	16.803	58.227	31.021	7.419	60.804
sd	4.024	3.848	5.869	13.011	3.421	4.024
median	65	16	58	30	6.749	60
trimmed	65.621	16.642	58.157	29.029	6.933	60.621
mad	4.448	2.965	5.930	14.826	0.645	4.448
min	60	3	40	12	0.066	55
max	74	43	74	120	39.671	69
range	14	40	34	108	39.606	14
skew	0.310	0.994	0.072	1.411	2.492	0.310
kurtosis	−1.012	4.359	−0.431	2.820	10.793	−1.012
se	0.076	0.073	0.111	0.246	0.065	0.076

Note: Age at time of survey, Age at smoking onset, Age at smoking quit, Number of cigarettes per day, Total number of pack-years smoked, Lagged age. The table shows descriptive statistics of the main variables used in the TSCE calculations from the TSCE subset of the National Lung Screening Trial (NLST) dataset. Refer to Epidemiological Input Parameters for details.

Table A10: Lung cancer cases frequency data

Value	Frequency	Proportion
0	4,604	0.752
1	1,517	0.248

Note: The table shows the proportions of Confirmed Lung Cancer cases (1) and Confirmed Not Lung Cancer cases (0) in the National Lung Screening Trial (NLST) dataset subset used in the Two-Stage Clonal Expansion calculations.

Table A11: Frequency Data for the presence of nodal involvement and distant metastasis in the *National Lung Screening Trial (NLST)* dataset

Value	Frequency	Proportion	Variable
M0	1,261	0.743	clinical_m_7thed
M1	437	0.257	clinical_m_7thed
		1	
N0	993	0.585	clinical_n_7thed
N1	113	0.067	clinical_n_7thed
N2	434	0.256	clinical_n_7thed
N3	158	0.093	clinical_n_7thed
		1	

Note: Presence of distant metastasis, Extent of nodal involvement. The table shows the raw proportions of nodal involvement and distant metastasis in the NLST dataset. Different from calibration targets, refer to Table 12.

Table A12: Descriptive Statistics of PLCOm2012 score continuous inputs

	BMI	Number of cigarettes	Years of smoking	Time since smoking quit	Pack-years
n	9,376	9,414	9,414	9,414	9,414
mean	27.609	28.825	41.099	3.564	58.681
sd	4.884	11.660	7.485	4.871	25.430
median	27.116	25	41	0	51
trimmed	27.260	27.078	41.131	2.736	54.887
mad	4.307	7.413	7.413	0	19.274
min	14.205	11	15	0	29
max	65.007	120	67	29	260
range	50.802	109	52	29	231
skew	0.915	1.609	−0.058	1.090	1.788
kurtosis	1.943	3.727	0.008	−0.197	4.933
se	0.050	0.120	0.077	0.050	0.262

Note: This table presents descriptive statistics of the continuous variables body mass index, Average number of cigarettes smoked per day, Total number of smoking years, Time since smoking quit, Total number of pack-years smoked. The table shows descriptive statistics of the main continuous variables used in the PLCOm2012 score calculations from the PLCOm2012 subset of the National Lung Screening Trial (NLST) dataset. Refer to R Source Code.

Table A13: Descriptive Statistics of PLCOm2012 score discrete inputs

Value	Frequency	Proportion	Variable
1	8,773	0.932	race
2	336	0.036	race
3	24	0.003	race
4	243	0.026	race
5	38	0.004	race
		1	
1	639	0.069	educat
2	2,433	0.263	educat
3	1,419	0.153	educat
4	2,117	0.229	educat
5	2,645	0.286	educat
		1	
0	8,816	0.937	diagcopd
1	588	0.063	diagcopd
		1	
0	8,938	0.949	cancer_hist
1	476	0.051	cancer_hist
		1	
0	7,337	0.779	family_hist
1	2,077	0.221	family_hist
		1	
0	4,753	0.505	cigsmok
1	4,661	0.495	cigsmok
		1	

Note: This table presents descriptive statistics of the discrete variables ethnicity of the individual, level of education, Chronic Obstructive Pulmonary Disease (COPD) diagnosis prior to trial, Personal history of any cancer, Family history of lung cancer, Smoking status of the individual (1 for smokers and 0 for ex-smokers). The table shows frequency data of the main discrete variables used in the PLCOm2012 score calculations from the PLCOm2012 subset of the National Lung Screening Trial (NLST) dataset. Refer to R Source Code.

Table A14: Sensitivity and Specificity by Volume Sizes

Volume Size Range	Sensitivity	Specificity
$y_t \geq 33.51032$	0.600	0.980
$33.51032 < y_t \leq 268.0826$	0.770	0.980
$y_t >$268.0826	1	0.980

Note: This table presents the sensitivity and specificity values by tumour volume size (y_t) used in our model

Table A15: Cost and Input Values

Utilities	Value	Costs	Value (2023NOK)
Utility decrement Stage I	0.991	End-of-life cost	219,998.600
Utility decrement Stage II	0.942	Cost of Stage I	204,025.300
Utility decrement Stage III	0.942	Cost of Stage II	227,414.900
Utility decrement Stage IV	0.930	Cost of Stage III	318,577.800
Utility in death state	0	Cost of Stage IV	370,400.700
Disutility due to primary screening	0.010	Cost of primary screening	3,280.031
Disutility due to follow-up screening	0.010	Cost of follow-up screening	3,280.031
Disutility due to false positive screening	0.063	Cost of false positive screening	8,996.069
Disutility due to diagnostic workup	0.063	Cost of diagnostic workup - symptom detected	18,927.840
		Cost of diagnostic workup - screening detected	15,647.810

Note: The left part of the table presents the utility decrements for diagnosed lung cancer stages, relatively to the background utility value and the disutilities due to screening and dianogstic procedures. The right part of the table presents costs by diagnosed stage of lung cancer and additional costs due to sreening. For more information on how these values were used please refer to the Cost-Effectiveness Analysis section.

Table A16: Averted Deaths

Scenario	Number of Deaths - No Screening	Number of Death - Screening	Averted Deaths	Percent reduction
Base Case	470	437	33	7.0%
Scenario 1	470	444	26	5.5%
Scenario 2	470	449	21	4.5%
Scenario 3	470	441	29	6.2%
Scenario 4	470	458	12	2.6%
Scenario 5	470	441	29	6.2%

Note: This table shows the total number of deaths due to lung cancer among the No Screening and the different scenarios. The difference between them is the number of averted deaths due to screening.