# A preliminary cost-effectiveness analysis of the You2yourself health monitor for earlier detection of lung cancer

Submission Date: 20-08-2021

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**ABSTRACT**

Many chronic diseases are detected at an advanced stage, which potentially leads to low survival rates and higher healthcare costs. This generally happens because people visit the doctor when they have complaints and that sometimes means that the disease is already in an advanced stage. This is for example the case with lung cancer, where 50% of the cases are detected at stage IV. In order to detect diseases at an earlier stage, the You2yourself health monitor was developed. Since this health monitor is still in its infancy, its potential cost-effectiveness is unknown.

To determine the potential cost-effectiveness of the health monitor, a Markov model was developed for the disease lung cancer with a lifelong time horizon and a cycle length of 6 months. An optimistic scenario (80% of lung cancer cases are detected at stage I-II, 10% at stage III, and 10% at stage IV) and a pessimistic scenario (30% of the lung cancer cases are detected at stage I-II, 40% at stage III, and 30% at stage IV) was developed to estimate the cost-effectiveness compared to the standard care (where 25% of the cases are detected at stage I-II, 25% at stage III, and 50% at stage IV). The outcomes were costs, quality-adjusted life years (QALYs), and life years (LY). A one-way deterministic and a probabilistic sensitivity analyses were conducted to assess the impact of uncertainty on the results.

The monitoring led to an increase in costs of €10,520 in the optimistic scenario and €10,584 in the pessimistic scenario. The incremental QALYs are 0.16 in the optimistic scenario and 0.02 in the pessimistic scenario. Thus, the incremental cost-effectiveness ratios (ICER) are €67,367 and €688,388 per QALY in the optimistic and pessimistic scenario, respectively.
In conclusion, the health monitor seems cost-effective in the optimistic scenario at a willingness-to-pay (WTP) of €80,000/QALY. This means that only when the health monitor detects a considerably large number of patients (80%) at stage I-II, the health monitor would seem to be cost-effective. As a recommendation, it would be useful to know what the minimum number of people is that should be detected at stage I-II for the health monitor to be considered cost-effective. Therefore, different scenarios with different lung cancer stage distributions could be investigated to determine that.

**KEYWORDS**

Lung cancer, cost-effectiveness, health monitor, health state transition model, sensitivity analysis.

## 1 INTRODUCTION

Chronic diseases, such as cardiovascular diseases and cancer, are the leading causes of death in the Netherlands (1). They are also the leading drivers of increasing healthcare costs (2). Due to aging and increasing life expectancy of the population, the number of chronic disease patients is expected to increase (3), and that leads to higher healthcare costs for the society (4).

Generally, people pay a visit to the general practitioner (GP) when they start having health complaints. This tends to happen when the chronic disease is already in an advanced stage. This is for example the case with lung cancer, where 50% of lung cancer patients are diagnosed at stage IV according to the Dutch cancer registration (5). For lung cancer disease, which is one of the leading causes of death in the Netherlands, there are currently no screening programs available (1). Patients diagnosed at that advanced stage have a low survival rate, and the healthcare costs are considerably high. As such, it is imperative that a solution must be found to reduce the healthcare costs and the number of patients diagnosed at advanced stages. As people are becoming increasingly conscious about monitoring their health in different forms like total body scans and wearable devices, it would be innovative to introduce a health monitor to solve the current problem. Nowadays, many people will be interested to monitor their health continuously. With this ideology in mind, the You2Yourself health monitor was developed to counteract the late diagnosis of chronic diseases (6). The aim of this monitor is to detect chronic diseases at an early stage through periodic urine analysis.

The principle behind this monitor is that it measures the changes of the microRNAs (miRNAs) in urine. MiRNAs are biomarkers present in blood and urine that can serve as indicators for a specific disease (7). Previous research has proven that the miRNA profile of an individual changes during the onset of a disease before any symptoms occur (8).
The concentration of miRNA's is determined by Next Generation Sequencing (NGS) (6). At first, the baseline of the miRNA concentrations should be determined for each individual. This will be done by delivering urine every three months in the first year of monitoring. Thereafter, each individual will deliver his urine every six months for analysis to determine any abnormal changes in the miRNA profile. If there were to be, the individual will receive a recommendation to visit the GP for a checkup. Ideally, the disease should then be at an early curable stage.

Hypothetically, the health monitor can detect all forms of cancer, cardiovascular diseases, and neurological diseases (6). Although this sounds promising, there will always be a certain amount of costs involved. Furthermore, it is also important to see what benefits there is to gain in terms of health and earlier diagnoses of diseases. Since the health monitor is still in the development phase, its sensitivity, specificity, and effectiveness, *i.e.* the number of people diagnosed at an early stage, are still unknown.
Therefore, a cost-effectiveness analysis should be conducted to determine the potential cost-effectiveness of this health monitor for the Dutch society. Moreover, the cost-effectiveness analysis will give insight into how effective the health monitor should be to be considered cost-effective.

The study will focus on lung cancer and the aim is to evaluate the potential cost-effectiveness of the You2yourself health monitor in early detection of lung cancer for individuals from the age of 40, compared to standard care (no monitoring).

## 2 METHOD

### 2.1 Model structure

To determine the potential cost-effectiveness of the health monitor and to answer the research question, a Markov model was developed. Markov models are useful to model prognosis for decision problems with ongoing risk like lung cancer, where the risk of developing lung cancer is ongoing throughout the lifetime. It also allows estimating the lifetime costs and effects (9). The Markov models in Figure 1 A and B simulates the clinical path and health states a

cohort of individuals will go through when being monitored and when not.

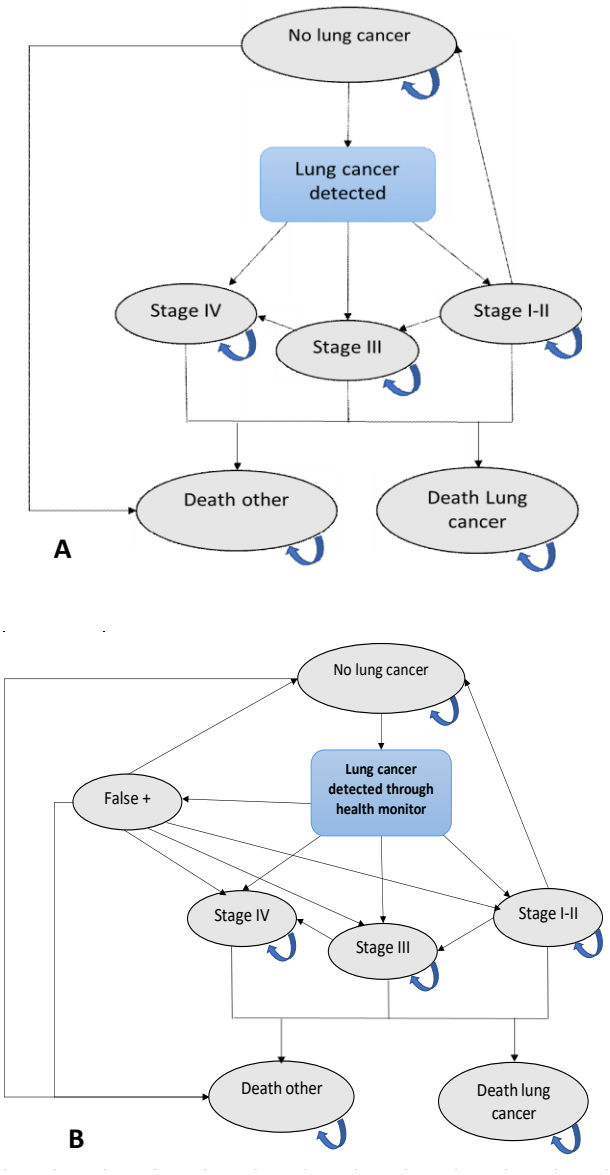


**Figure 1 A and B Markov model standard care vs health monitoring application**

**Not monitored cohort:** Figure 1.A illustrates the standard care situation (no monitoring) where patients visit the GP when experiencing complaints. Starting from healthy (no apparent lung cancer), individuals can stay in the same health state or transit to lung cancer stage I-II, III, or IV. Lung cancer stages I and II are taken together because theses stages often overlap. Individuals in stage I-II can possibly return to the no lung cancer state because the cancer is curable in these stages (10). However, there is no evidence from literature that cancer stages III and IV can return to no lung cancer state. Therefore, there was no possibility to return from cancer stage III or IV to no lung cancer in this model.

**Monitored cohort:** Figure 1.B shows the Markov model when monitoring is applied. Individuals can transit from no lung cancer to the different lung cancer stages or to the false positive state.

This additional health state was added since monitored individuals can receive a positive result while the disease is not present. Based on a previous research that examined the sensitivity and the specificity of NGS (11), it was assumed that 2% of the monitored individuals will receive a false positive result. This means that the specificity of the health monitor is 98%.

No false negative health state was included since literature showed no difference in costs nor quality of life for individuals with false negative results (12).

All individuals in each health state, including the lung cancer and false positive states, will be monitored throughout their lifetime. This will also be the case in reality since people who develop lung cancer will remain monitored in case they develop another disease that can be detected by the monitor. Thus, individuals who develop lung cancer or receive a false positive result will continue to be monitored and therefore one can also transit from the false positive state to a lung cancer stage.

Monitored individuals have similar probability to develop lung cancer as the not monitored individuals, only a downward stage shift was applied (13), *ie*, the health monitor is expected to alter the cancer stage distribution so that lung cancer is diagnosed earlier than in the standard care cohort. Therefore, an optimistic and a pessimistic scenario with different cancer stage distributions were created to estimate the cost-effectiveness of the health monitor.

The current lung cancer stage distribution is as follows: 25% is detected at stages I-II, 25% at stage III, and 50% is detected at stage IV (5). In the

optimistic scenario, it was assumed that 80% of the patients will be detected at stage I-II, 10% at stage III, and 10% at stage IV. Since 80% of the lung cancer patients will be detected at stage I-II, this means that the monitor's sensitivity in detecting early stage lung cancer is 80%.

In the pessimistic scenario, it was assumed that the monitor is less sensitive in detecting early stages and will thus detect 30% at stage I-II, 40% at stage III, and 30% at stage IV. This means that the monitor's sensitivity in detecting early stage lung cancer is 30%.

In both monitored and not monitored cohorts, lung cancer progression was taken into consideration, thus individuals could transit to an advanced stage or stay in the same stage.

All individuals in each health state could transit to the death state due to reasons other than lung cancer death. Besides, lung cancer patients in each stage could transit to death due to lung cancer.

**2.2 Population and outcomes**

Developing lung cancer is rare in individuals that are below the age of 40 (14), thus the chosen population's starting age was 40 years. The considered population is not a high risk population and as such, it will represent a more realistic scenario of when the health monitor is implemented. When implemented, all individuals, not only high risks, can be admitted to monitor their health. As such, a hypothetical population of 1,000 healthy individuals aged 40 years was considered for the Markov model. The model was based on a societal perspective. A lifelong time horizon was applied and the cycle length was six months. This cycle length was chosen to resemble the period that the individuals will deliver their urine for monitoring.

The primary outcomes of the analysis are costs, quality-adjusted life years (QALY), and life years (LY). These outcomes were used to calculate the total costs and effects and subsequently the incremental cost-effectiveness ratio (ICER) of each scenario. The costs were discounted at a rate of 4%, and the QALYs and life years gained were discounted at 1.5% according to the Dutch guidelines for economic evaluation in healthcare (15).

The health monitor was considered cost-effective if the ICER was below the threshold of €80,000 per QALY for high burden diseases, according to the Dutch National Health Care Institute (16).

All the analyses were performed in Microsoft Excel 2016.

**2.3 Model parameters**

Transition probabilities were assigned to the Markov model health states to show the transitioning from one state to another. Each health state was also assigned a cost and a utility value.

The transition probabilities of lung cancer were obtained from The Dutch Cancer Registry (IKNL) (17). The cancer stage distribution percentages were multiplied by the probability of developing lung cancer to obtain the transition probability from lung cancer to the different stages.
The mortality probabilities attributable to lung cancer and/or other causes were derived from the Dutch central office for statistics (CBS) (18). Age-dependent variables, such as lung cancer mortality and other-cause mortality, were taken into consideration. This means that the probability of death increases as the cohort ages.

The probabilities were adjusted to ensure that they fit the cycle length. Therefore, the probabilities were converted into half-year probabilities by converting the probability into a rate using the formula:

$$p = 1 - e^{-rt} \qquad (19)$$

Then the rate is translated into a transition probability using the formula:

$$r = -\frac{1}{t} ln\,(1 - p) \qquad (19)$$

An overview of the half-year probabilities and the annual costs and utilities are shown in Table 1:

**Table 1 Input parameters probabilities**

| *Probabilities* | *Value* | *SE* | *Distribution* | *Ref.* |
|---|---|---|---|---|
| **Strategy independent value** | | | | |
| No lung cancer-Lung cancer | 0.00075 | 0.00015* | Beta | Calculated based on (14)(17) |
| Death other | Varies with age | - | - | (18) Appendix 1 |
| Death lung cancer | Varies with age | - | - | (13) Appendix 2 |
| Stage I-II - No lung cancer | 0.337 | 0.0674* | Beta | Assumption (10) |
| Stage I-II - Stage III | 0.261 | 0.1 | Beta | (20) |
| Stage III - Stage IV | 0.318 | 0.1 | Beta | (20) |
| Lung cancer – False + | 0.02 | 0.004* | Beta | (11) |
| | | | | |
| **Standard care** | | | | |
| Lung cancer – Stage I-II | 0.00019 (25%) ** | - | - | Calculated based on (5) |
| Lung cancer – Stage III | 0.00019 (25%) ** | - | - | Calculated based on (5) |
| Lung cancer – Stage IV | 0.00037 (50%) ** | - | - | Calculated based on (5) |
| | | | | |
| **Optimistic scenario** | | | | |
| Lung cancer – Stage I-II | 0.0006 (80%) ** | - | - | Assumption |
| Lung cancer – Stage III | 0.000075 (10%) ** | - | - | Assumption |
| Lung cancer - Stage IV | 0.000075 (10%) ** | - | - | Assumption |
| False + - Stage I-II | 0.0006 (80%) ** | - | - | Assumption |
| False + - Stage III | 0.000075 (10%) ** | - | - | Assumption |
| False + - Stage IV | 0.000075 (10%) ** | - | - | Assumption |
| | | | | |
| **Pessimistic scenario** | | | | |
| Lung cancer – Stage I-II | 0.000225 (30%) ** | - | - | Assumption |
| Lung cancer – Stage III | 0.0003 (40%) ** | - | - | Assumption |
| Lung cancer – Stage IV | 0.000225 (30%) ** | - | - | Assumption |
| False + - Stage I-II | 0.000225 (30%) ** | - | - | Assumption |
| False + - Stage III | 0.0003 (40%) ** | - | - | Assumption |
| False + - Stage IV | 0.000225 (30%) ** | - | - | Assumption |

| | *Value* | *SD* | *Distribution* | *Ref.* |
|---|---|---|---|---|
| ***Costs within healthcare system*** | | | | |
| Stage I-II | €16,077 | €5,086 | Gamma | (21) |
| Stage III | €16,077 | €5,086 | Gamma | (21) |
| Stage IV | €33,456 | €5,582 | Gamma | (21) |
| | | | | |
| ***Costs for patient and caregiver before retirement*** | | | | |
| Stage I-II | €3,858 | €772* | Gamma | (22) |
| Stage III | €6,105 | €1,221* | Gamma | (22) |
| Stage IV | €13,996 | €2,799* | Gamma | (22) |
| | | | | |
| ***Costs for patient and caregiver after retirement*** | | | | |
| Stage I-II | €2,679 | €536* | Gamma | (22) |
| Stage III | €3,728 | €746* | Gamma | (22) |
| Stage IV | €9,991 | €1,998* | Gamma | (22) |
| | | | | |
| ***Monitoring costs*** | | | | |
| Baseline costs (first year) | €800 | €160* | Gamma | Estimate |
| Costs after the first year | €500 | €100* | Gamma | Estimate |
| False + | €2,025 | €1,503 | Gamma | (21) |
| | | | | |
| ***Utility*** | | | | |
| No lung cancer | 0.89 | 0.18 | Beta | (23) |
| Stage I-II | 0.76 | 0.24 | Beta | (24) |
| Stage III | 0.7 | 0.29 | Beta | (24) |
| Stage IV | 0.53 | 0.36 | Beta | (13) |
| False + | 0.89 | 0.18 | Beta | (23) |

** Standard deviation (SD)/Standard error (SE) value is assumed to be 20% of the mean value*

*** Value is obtained by multiplying the mentioned percentage by the half-year probability of developing lung cancer (0.00075)*

### 2.3.1 Costs

Both costs within the healthcare system and costs for patient and caregiver were taken into account. The costs within the healthcare system were obtained from a Dutch study that captured the medical costs of all stages of lung cancer in the Netherlands (21). These costs included surgeries, radiotherapy, chemotherapy, laboratory tests, medical imaging services, medical diagnostics and procedures, in-patient hospital days, outpatient visits, consultations, day care visits, hospitalizations and intensive care stay.

The costs of a false positive result were also derived from this study and these costs include diagnosis costs such as laboratory tests and medical imaging and procedures.

For the costs for patient and caregiver, these costs included wage loss, non-medical expenses associated with general practitioner or hospital visits, secondary lung cancer-related treatment costs such as pain or symptom relief treatments, additional childcare costs, assistance at home, and travel costs (22).

Besides, productivity loss due to illness was taken into account for the patients and caregivers (22). After the retirement age of 67, productivity loss was not included.

All costs were indexed to 2020 prices using the consumer price index provided by the Dutch central bureau of statistics (CBS) (25).

### 2.3.2 Quality of life

Health state utilities were based on previous research where utility was elicited through EQ-5D questionnaires. The utility for individuals with no lung cancer was obtained from a study that elicited the age-dependent utility values of the general population through EQ-5D questionnaire in 18 different countries, among which the Netherlands (23).

The utility of patients in different lung cancer stages was obtained from another Dutch study that elicited these utilities through EQ-5D questionnaire (24).

Research showed no significant disutility related to false positive results (26) (27), for this reason, the utility of false positive was similar to the utility of no lung cancer.

### 2.4 Sensitivity analysis

To reflect uncertainties in the model parameter estimates and to examine the robustness of the model, a one-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) were conducted for the optimistic and the pessimistic scenario versus the standard care scenario (28).

Given the level of uncertainty about the specificity of monitoring, this analysis also examined the effect of false positive results on the cost-effectiveness of the health monitor. The false positive rate was varied separately between 1% and 40% and its effect on the total and incremental costs and QALYs and on the ICER was determined.

For the one-way sensitivity analysis, the value of one parameter was varied at a time and its effect on the ICER was examined.

The parameters with known SE were varied over their 95% confidence intervals. The parameters with unknown SE, *i.e.* patient and caregiver costs and stage distribution parameters were also varied over their 95% confidence interval and the SE was assumed to be 20% of the mean value (29).

The ten parameters that had the greatest effect on the model output were demonstrated in a figure.

Subsequently, PSA was conducted in the form of a Monte Carlo simulation. Monte Carlo simulation is a mathematical technique that models uncertainties (30). It assigns each input parameter a random value based on a pre-defined parameter distribution, the simulation is then run and a result is calculated. This process is repeated multiple times while assigning a different random value to each input parameter every time. A total of 1,000 runs were performed in this analysis. The transition probabilities and utility values were randomly drawn from beta distributions, while the cost values were drawn from gamma distributions (Table 1). The lung cancer distribution probabilities have been kept fixed.

A cost-effectiveness acceptability curve (CEAC) was also drawn to show the probability of the health monitor being cost-effective compared to standard care at WTPs ranging from €0 to €100,000 per QALY.

## 3 RESULTS

### 3.1 Markov model deterministic results

The deterministic results showed a total costs per person of €680 in the standard care cohort. In the

optimistic and pessimistic cohort simulation, the costs per person are €11,200 and €11,264, respectively.

The introduction of the health monitor showed an incremental gain of 0.16 QALYs per person in the optimistic scenario and an incremental gain of 0.02 QALYs per person in the pessimistic scenario. Furthermore, a gain of 0.17 and 0.02 life years was shown in the optimistic and pessimistic scenario, respectively. The incremental costs of monitoring are €10,520 in the optimistic scenario and €10,584 in the pessimistic scenario. The ICERs are therefore €67,367 and €688,388 per QALY for the optimistic and pessimistic scenario, respectively (Table 2).

**Table 2 Deterministic outcomes of the Markov model**

| | ***Costs (increment)*** | ***QALYs (increment)*** | ***Life years gained (increment)*** |
|---|---|---|---|
| ***Standard care*** | 680 | 26.42 | 29.70 |
| ***Optimistic scenario*** | 11,200 (10,520) | 26.58 (0.16) | 29.87 (0.17) |
| ***Pessimistic scenario*** | 11,264 (10,584) | 26.44 (0.02) | 29.72 (0.02) |
| | | | |
| | **Optimistic scenario** | **Pessimistic scenario** | |
| ***ICER (Euros/QALY)*** | 67,367 | 688,388 | |

### 3.2 One-way sensitivity analysis

False positive rates were varied between 1% and 40% and their effect on the model outcomes is shown in Table 3:

**Table 3 Outcomes of the model when different false positive rates are applied**

| | ***Optimistic scenario*** | | | ***Pessimistic scenario*** | | |
|---|---|---|---|---|---|---|
| ***False + rate*** | **Costs (increment)** | **QALY (increment)** | **ICER** | **Costs (increment)** | **QALY (increment)** | **ICER** |
| **1%** | 10,815 (10,135) | 26.6 (0.16) | 64,900 | 10,881 (10,200) | 26.4 (0.02) | 663,439 |
| **2% (base case)** | 11,200 (10,520) | 26.6 (0.16) | 67,367 | 11,264 (10,584) | 26.4 (0.02) | 688,388 |
| **5%** | 12,312 (11,632) | 26.6 (0.16) | 74,490 | 12,372 (11,692) | 26.4 (0.02) | 760,438 |
| **10%** | 14,034 (13,354) | 26.6 (0.16) | 85,514 | 14,087 (13,406) | 26.4 (0.02) | 871,946 |
| **20%** | 17,054 (16,373) | 26.6 (0.16) | 104,852 | 17,094 (16,414) | 26.4 (0.02) | 1,067,554 |
| **40%** | 21,818 (21,138) | 26.6 (0.16) | 135,361 | 21,839 (21,159) | 26.4 (0.02) | 1,376,162 |

Increasing the false positive rate results in increased total costs in both scenarios while the total QALYs stays similar. The ICERs in both scenarios therefore increases with increasing false positive rate.

The results of the one-way sensitivity analysis are represented in Figures 2 and 3.

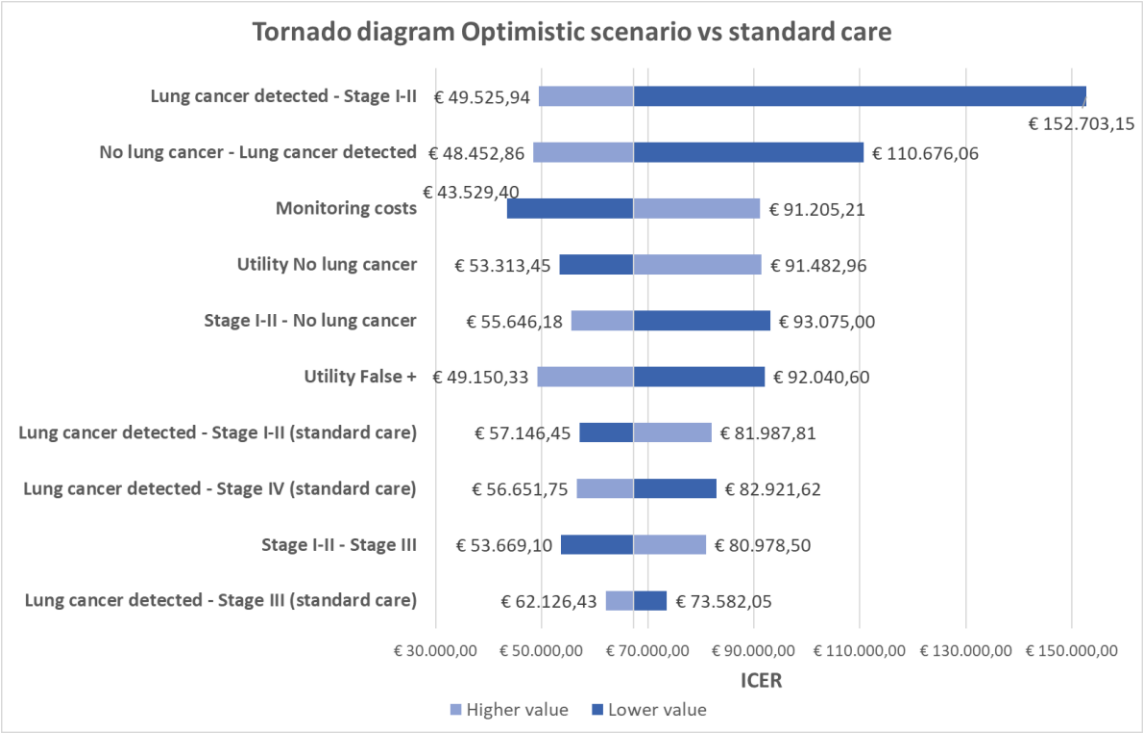


Figure 2 Tornado diagram optimistic scenario

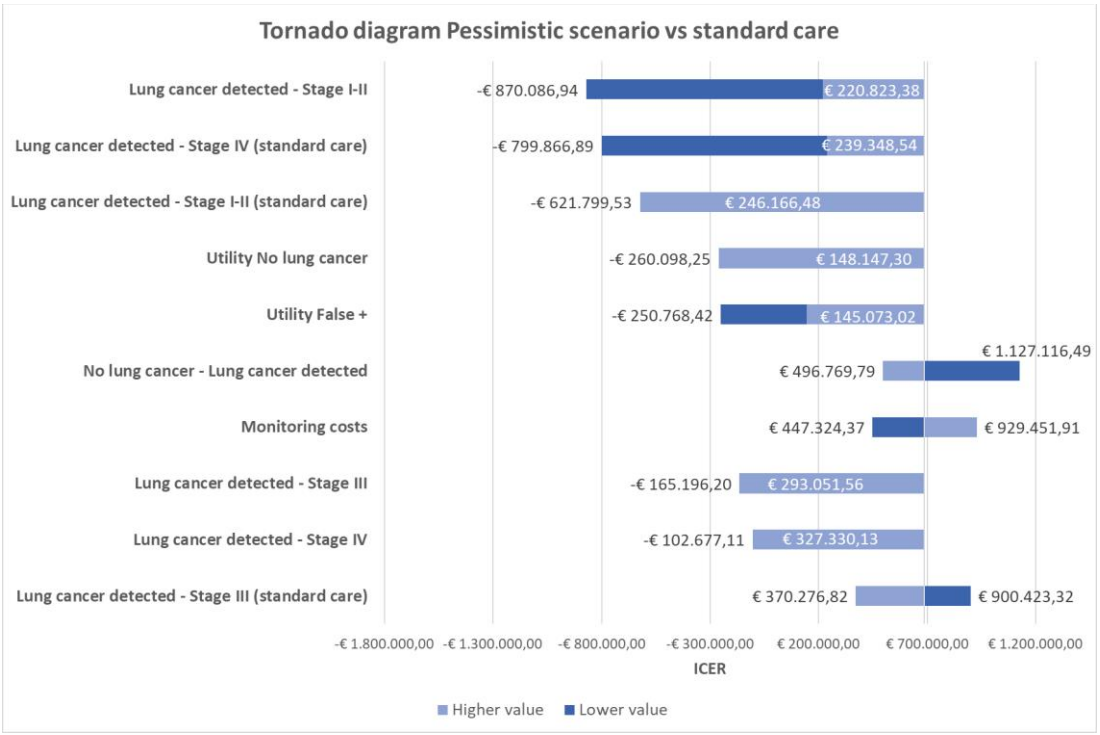


Figure 3 Tornado diagram pessimistic scenario

In the optimistic scenario, the parameters with the greatest effect on the ICER are the transition probability from no lung cancer to stage I-II, probability of developing lung cancer, and monitoring costs. Varying the transition probability from no lung cancer to lung cancer stage III in the standard care cohort had little effect on the ICER (Figure 2).
In the pessimistic scenario, varying the transition probability from no lung cancer to lung cancer stage I-II in the pessimistic scenario had the greatest effect on the ICER. Besides, varying the transition probability from no lung cancer to lung cancer stage I-II and IV in the standard care cohort also had a great effect on the ICER. Varying the transition probability from no lung cancer to lung cancer stage III in the standard care cohort had little effect on the ICER (Figure 3).

### 3.3 Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are listed in Table 4:

**Table 4 Incremental outcomes sensitivity analysis**

| | **Costs** | **QALYs** | **Life years gained** |
|---|---|---|---|
| **Standard care** | 682 | 26.35 | 29.70 |
| **Optimistic scenario** | 11,182 | 26.51 | 29.87 |
| **Pessimistic scenario** | 11,231 | 26.37 | 29.71 |
| | **Incremental costs (95%-CI)*** | **Incremental QALYs (95%-CI)*** | **Incremental Life years (95%-CI)*** |
| **Optimistic scenario** | 10,500 (6,793- 14,640) | 0.16 (0.04- 0.4) | 0.17 (0.1- 0.27) |
| **Pessimistic scenario** | 10,549 (6,916- 14,834) | 0.02 (0.008- 0.022) | 0.02 (0.01- 0.02) |
| | | | |
| | **Optimistic scenario** | **Pessimistic scenario** | |
| **ICER (Euros/QALY)** | 66,187 | 623,320 | |

** 95%- confidence interval*

The results show that the incremental costs and QALYs in the optimistic scenario are €10,500 and 0.16, respectively. The ICER is therefore €66,187/QALY in the optimistic scenario. The incremental costs and QALYs in the pessimistic scenario are €10,549 and 0.02, respectively and the ICER is €623,320/QALY.

The results of the PSA are also shown in the incremental cost-effectiveness planes in Figures 4 and 5.

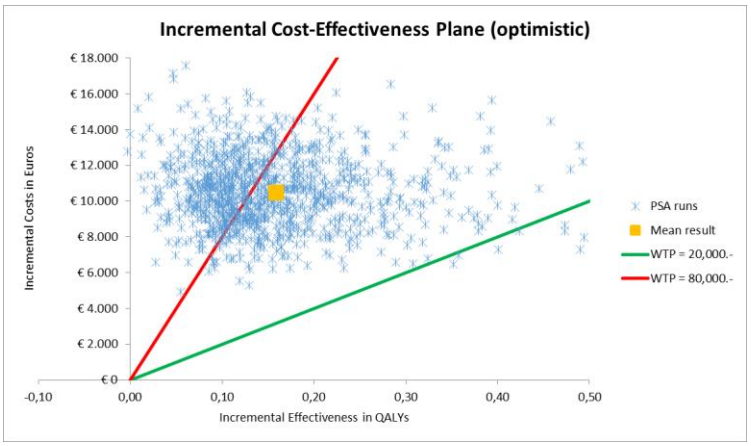


**Figure 4 ICE plane optimistic scenario**

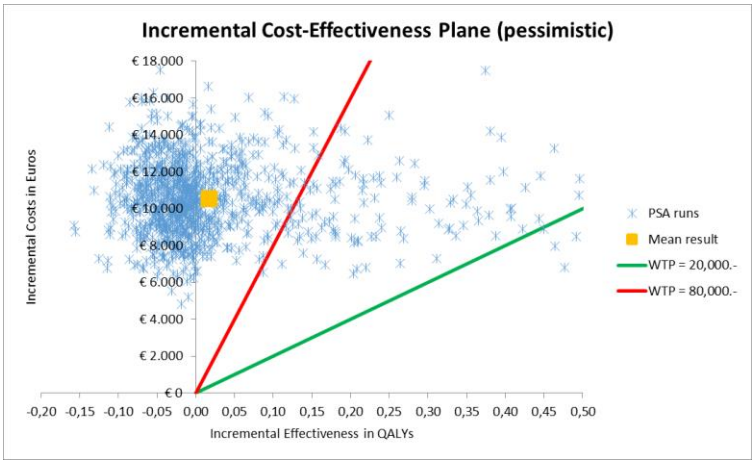


**Figure 5 ICE plane pessimistic scenario**

The red line represents the WTP threshold of €80,000/QALY. As seen, most of the outcomes of the optimistic scenario are below this threshold. In the pessimistic scenario, most of the outcomes are above this threshold.

The CEAC of the two different scenarios are shown in figures 6 and 7.

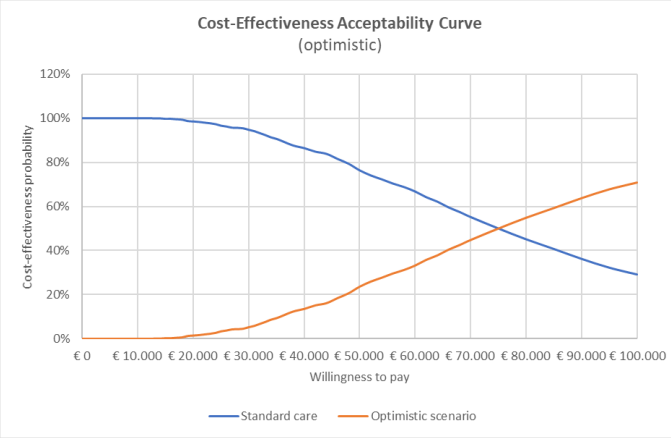


**Figure 6 CEAC optimistic scenario**

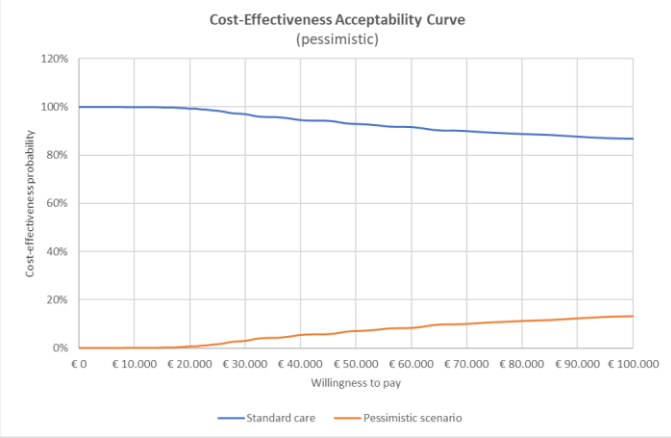


**Figure 7 CEAC pessimistic scenario**

The results of the optimistic scenario show that at a WTP of €20,000/QALY, the probability of the health monitor being cost-effective is 0.015%. At a WTP of €80,000/QALY, this probability is 55% (Figure 6).

In the pessimistic scenario, the cost-effectiveness acceptability curve shows that the probability of the health monitor being cost-effective is 0.007% at a WTP of €20,000/QALY. At a WTP of €80,000/QALY, this probability is 11% (Figure 7).

## 4 DISCUSSION

In this study, a Markov model was developed to assess the potential cost-effectiveness of the You2yourself health monitor in the early detection of lung cancer. This is the first preliminary cost-effectiveness analysis of this health monitor. The results showed that the adoption of the You2yourself health monitor will potentially lead to higher costs but also to QALY gain, compared to the standard care where no monitoring or screening is applied. The ICER in the optimistic scenario is €67,367/QALY and the ICER in the pessimistic scenario is €688,388/QALY.

In the optimistic scenario, it was assumed that 80% of the individuals that develop lung cancer will be diagnosed at stage I-II. The results of the optimistic scenario show that the health monitor seems to be cost-effective at a WTP of €80,000/QALY. This means that when a large number of lung cancer patients are detected at an early stage (I-II), the monitor would be considered cost-effective. On the other hand, in the pessimistic scenario it was assumed that 30% of the patients will be detected at stage I-II. This number is slightly higher than the number diagnosed currently at stage I-II without monitoring (25%). The probabilities of being detected at stages III and IV also did not differ much from the current probability, thus the incremental QALY gain was low (0.02). The health monitor does not seem to be cost-effective at a WTP of €80,000/QALY in the pessimistic scenario. Practically, this means that if the health monitor does not detect a high number of patients at an early stage, the health monitor would not be considered cost-effective. In reality, it is uncertain whether these assumptions are valid. The health monitor is currently in a clinical research stage and the results of this research will give better insight into how sensitive the health monitor is in early detection and a better estimate of the ICER can be obtained.

Several cost-effectiveness analyses on lung cancer screening programs have been conducted so far. One of these studies is a German study by Hofer *et al.* that reported an ICER of €30,291 per QALY for annual

screening with low dose CT scan (31). The incremental costs were €1,153 and the incremental QALYs were 0.04 per person. Noticeably, the incremental screening costs were lower than the incremental costs found in this model (€10,520 and €10,584). This is because the CT scan costs (€99) are considerably lower than the monitoring costs (€500 after year one). Moreover, the costs were estimated from a public payer point of view, while in this study a societal perspective was chosen that included direct medical costs and costs for patient and caregiver.

Furthermore, the considered population was a high risk population, in contrast to this model. Focussing on high risk populations results in higher cost-effectiveness of the screening program, since the incremental effects would be higher. This was shown in another cost-effectiveness analysis for lung cancer screening where lower risk and high risk populations were both considered (13). It was concluded that the incremental effectiveness of screening increased with higher risk cohort.

In our study, it was not chosen for a high risk population since everyone will be eligible to monitor his/her health and not only the high risk individuals. This also explains the low total costs in the standard care cohort (€680 per person compared to €2,787 reported by Hofer *et al.*). Since the annual lung cancer incidence was low (0.15% while high risk lung cancer incidence is around 0.5%), fewer individuals developed lung cancer which means that the average incurred costs per person are low. If a lung cancer incidence of 0.5% would have been applied, the average costs per person would amount to €2,168 in the standard clinical care cohort, which is close to the costs found by Hofer *et al.* Besides, applying a lung cancer incidence of 0.5% would result in an incremental QALYs of 0.5 and 0.05 and an ICER of €20,364/QALY and €212,141/QALY the optimistic and pessimistic scenario, respectively. This confirms the finding that considering a high risk population increases cost-effectiveness.

Since the health monitor is still not implemented, it can still be chosen to restrict participation only to high risk individuals to increase the incremental effectiveness and thus the cost-effectiveness of the health monitor.

Another aspect to point out is that QALY gain found in the optimistic scenario (0.16) is high compared to the QALY gain found by Hofer *et al.* (0.04), even though they considered a high risk population (31). This is because of the difference in screening's sensitivity in early detection of both methods. It was assumed that 80% of the patients will be detected at stage I-II, while in Hofer *et al.* study this percentage was only 40%, which means that fewer patients are detected at an early stage. Thus, the QALY gain in our study was considerably higher than in the other study. However, the QALY gain in the pessimistic scenario was 0.02 which is lower than the QALY gain reported by Hofer *et al*. That is because it was assumed that a low percentage (30%) will be detected at stage I-II, thus fewer patients were detected at an early stage compared to Hofer *et al.* study.

Although CT screening seems less effective than monitoring (optimistic scenario), the ICER of CT screening is yet lower than the ICERs reported in this study and that is attributable to the lower costs of a CT scan compared to the health monitor and the consideration of a high risk population. Despite the fact that screening with CT scan is less expensive, screening with the health monitor is more patient-friendly since it only requires delivering urine twice a year, while CT scan requires a hospital visit and exposure to radiation. Besides, the health monitor is designed to detect many other diseases at the same time, which means that its effects are expected to be higher than the estimated effects in this model. For this reason, the cost-effectiveness in this model is probably an underestimation of reality and further research is needed to map the additional effects against the costs of the monitor. Currently, there is no specific technique to evaluate the cost-effectiveness of a complex multicomponent intervention such as this health monitor. However, a study by Shiell *et al.* suggests specifying the inputs and outcomes of the multicomponent intervention with sufficient clarity to be able to measure and value the resource use and benefits in a cost-

effectiveness analysis (32). The study discussed the challenges around evaluating complex interventions and concluded that there are no new economic methods required only time, effort, and resources are required to evaluate all the components of the intervention in a single cost-effectiveness study.

After conducting the one-was sensitivity analysis, it was shown that varying the transition probability from no lung cancer to stage I-II had the highest impact on the ICER in both scenarios. Increasing the probability of early detection results in increased cost-effectiveness of the health monitor and vice versa. The lung cancer distribution probabilities always summed up to 100%, thus when increasing the probability of being detected at stage I-II, the probabilities of being detected at stage III and IV decreased to keep the overall percentage at 100%. For this reason, increasing the transition probability of being detected at stage I-II had the greatest effect on the ICERs, since it also means that fewer patients will be detected at advanced stages.
Varying the monitoring costs also had a considerable effect on both ICERs, since it resulted in a change of +/- 40% of the ICER in both scenarios.
Remarkably, the tornado diagram of the pessimistic scenario shifts to one side when varying certain lung cancer distribution parameters. This is for example the case when varying the transition probability of no lung cancer to stage I-II in the pessimistic cohort. When the probability of being diagnosed at stage I-II decreases, the total QALYs per person in the pessimistic scenario became lower than the total QALYs of the standard care cohort since fewer patients will be diagnosed at this early stage compared to the standard care. This results in a negative incremental QALY, which subsequently results in a negative ICER (appendix 3). Thus, a negative ICER means that the health monitor becomes less cost-effective.

Different false positive rates were examined and the results showed that the ICER increased by increasing false positive rates as expected. Receiving a false positive result is associated with additional diagnosis costs which resulted in higher costs per QALY. It was shown that the health monitor seems to be cost-effective till a false positive rate of 5% at a WTP of €80,000/QALY in the optimistic scenario. False positive rates higher than 5% resulted in ICERs higher than the threshold of €80,000/QALY. This means that for the health monitor to be cost-effective, its specificity should be at least 95%, besides detecting a large number of lung cancer cases at an early stage.

The model has several limitations. First, for many parameters such as the probability of developing lung cancer and the costs for patient and caregiver, the standard error (SE) was unknown. For this reason, it was assumed that the SE was 20% of the value which means that the exact uncertainty around these values was not taken into account in the sensitivity analyses. This might impact the accuracy of the PSA results.
However, with the current results it can be concluded that the model is considered robust, since the average outcomes of the PSA are consistent with the deterministic results and led to a similar conclusion regarding the cost-effectiveness of the health monitor.

Second, the probability of developing lung cancer increases with increasing age. However, this was not accounted for in the model and a mean probability of lung cancer development (independent of age) was used. If an increasing probability would have been assumed, the total number of individuals that developed lung cancer might differ, and this might results in a different ICER in both situations.
Third, due to lack of data, the out-of-pocket costs (costs for patient and caregiver) used in this model are costs estimated in the European countries France, Germany, and Italy. However, according to literature it was shown that the costs for patient and caregiver in the Netherlands are higher than these costs in France, Germany, and Italy (33). This means that the costs for patient and caregiver were underestimated in this model and thus the estimated total costs are lower than in reality.
At last, in the health monitoring scenarios it was assumed that individuals are 100% adherent to monitoring. This is not likely to be the case in reality, and lower adherence would lead to lower cost-

effectiveness of the health monitor. Thus, to obtain a better estimate of the cost-effectiveness of the health monitor, adherence should be taken into account.

In summary, the health monitor seems to be cost-effective for lung cancer detection only when most of the patients (80%) are diagnosed at an early stage (stage I-II) and when the specificity of the monitor is high (>5%).
As a recommendation, the health monitor could be implemented for high risk individuals to assure a higher cost-effectiveness of the monitor.

As follow-up research, different scenarios with different lung cancer stage distributions could be investigated to determine the minimum effectiveness of the health monitor to be considered cost-effective.

**ACKNOWLEDGMENTS**

I would like to thank my supervisors Dr. Xavier Pouwels and Dr. Karin Oudshoorn for all the help and supervision during the period of my thesis. I would also like to thank Bram de Moor and Johan de Rooij for giving me the opportunity to do my Master thesis at You2yourself.
Special thanks to my family and friends who supported me a lot during this period.

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## Appendix 1

Mortality probability of death other than lung cancer

| Age | Annual mortality (death other) | half year mortality (death other) |
|---|---|---|
| 40 | 0,00095 | 0,000475113 |
| 40,5 | 0,00095 | 0,000475113 |
| 41 | 0,00095 | 0,000475113 |
| 41,5 | 0,00095 | 0,000475113 |
| 42 | 0,00095 | 0,000475113 |
| 42,5 | 0,00095 | 0,000475113 |
| 43 | 0,00095 | 0,000475113 |
| 43,5 | 0,00095 | 0,000475113 |
| 44 | 0,00095 | 0,000475113 |
| 44,5 | 0,00095 | 0,000475113 |
| 45 | 0,00146 | 0,000730267 |
| 45,5 | 0,00146 | 0,000730267 |
| 46 | 0,00146 | 0,000730267 |
| 46,5 | 0,00146 | 0,000730267 |
| 47 | 0,00146 | 0,000730267 |
| 47,5 | 0,00146 | 0,000730267 |
| 48 | 0,00146 | 0,000730267 |
| 48,5 | 0,00146 | 0,000730267 |
| 49 | 0,00146 | 0,000730267 |
| 49,5 | 0,00146 | 0,000730267 |
| 50 | 0,00251 | 0,001255789 |
| 50,5 | 0,00251 | 0,001255789 |
| 51 | 0,00251 | 0,001255789 |
| 51,5 | 0,00251 | 0,001255789 |
| 52 | 0,00251 | 0,001255789 |
| 52,5 | 0,00251 | 0,001255789 |
| 53 | 0,00251 | 0,001255789 |
| 53,5 | 0,00251 | 0,001255789 |
| 54 | 0,00251 | 0,001255789 |
| 54,5 | 0,00251 | 0,001255789 |
| 55 | 0,00428 | 0,002142295 |
| 55,5 | 0,00428 | 0,002142295 |
| 56 | 0,00428 | 0,002142295 |
| 56,5 | 0,00428 | 0,002142295 |
| 57 | 0,00428 | 0,002142295 |
| 57,5 | 0,00428 | 0,002142295 |
| 58 | 0,00428 | 0,002142295 |
| 58,5 | 0,00428 | 0,002142295 |
| 59 | 0,00428 | 0,002142295 |
| 59,5 | 0,00428 | 0,002142295 |
| 60 | 0,00705 | 0,003531235 |
| 60,5 | 0,00705 | 0,003531235 |
| 61 | 0,00705 | 0,003531235 |
| 61,5 | 0,00705 | 0,003531235 |
| 62 | 0,00705 | 0,003531235 |
| 62,5 | 0,00705 | 0,003531235 |
| 63 | 0,00705 | 0,003531235 |
| 63,5 | 0,00705 | 0,003531235 |
| 64 | 0,00705 | 0,003531235 |
| 64,5 | 0,00705 | 0,003531235 |
| 65 | 0,01123 | 0,005630853 |
| 65,5 | 0,01123 | 0,005630853 |
| 66 | 0,01123 | 0,005630853 |
| 66,5 | 0,01123 | 0,005630853 |
| 67 | 0,01123 | 0,005630853 |
| 67,5 | 0,01123 | 0,005630853 |
| 68 | 0,01123 | 0,005630853 |
| 68,5 | 0,01123 | 0,005630853 |
| 69 | 0,01123 | 0,005630853 |
| 69,5 | 0,01123 | 0,005630853 |
| 70 | 0,01825 | 0,009167017 |
| 70,5 | 0,01825 | 0,009167017 |
| 71 | 0,01825 | 0,009167017 |
| 71,5 | 0,01825 | 0,009167017 |
| 72 | 0,01825 | 0,009167017 |
| 72,5 | 0,01825 | 0,009167017 |
| 73 | 0,01825 | 0,009167017 |
| 73,5 | 0,01825 | 0,009167017 |
| 74 | 0,01825 | 0,009167017 |
| 74,5 | 0,01825 | 0,009167017 |
| 75 | 0,03193 | 0,016094517 |
| 75,5 | 0,03193 | 0,016094517 |
| 76 | 0,03193 | 0,016094517 |
| 76,5 | 0,03193 | 0,016094517 |
| 77 | 0,03193 | 0,016094517 |
| 77,5 | 0,03193 | 0,016094517 |
| 78 | 0,03193 | 0,016094517 |
| 78,5 | 0,03193 | 0,016094517 |
| 79 | 0,03193 | 0,016094517 |
| 79,5 | 0,03193 | 0,016094517 |
| 80 | 0,05846 | 0,029670159 |
| 80,5 | 0,05846 | 0,029670159 |
| 81 | 0,05846 | 0,029670159 |
| 81,5 | 0,05846 | 0,029670159 |
| 82 | 0,05846 | 0,029670159 |
| 82,5 | 0,05846 | 0,029670159 |
| 83 | 0,05846 | 0,029670159 |
| 83,5 | 0,05846 | 0,029670159 |
| 84 | 0,05846 | 0,029670159 |
| 84,5 | 0,05846 | 0,029670159 |
| 85 | 0,11215 | 0,057742074 |
| 85,5 | 0,11215 | 0,057742074 |

| | | |
|---|---|---|
| 86 | 0,11215 | 0,057742074 |
| 86,5 | 0,11215 | 0,057742074 |
| 87 | 0,11215 | 0,057742074 |
| 87,5 | 0,11215 | 0,057742074 |
| 88 | 0,11215 | 0,057742074 |
| 88,5 | 0,11215 | 0,057742074 |
| 89 | 0,11215 | 0,057742074 |
| 89,5 | 0,11215 | 0,057742074 |
| 90 | 0,2074 | 0,109719145 |
| 90,5 | 0,2074 | 0,109719145 |
| 91 | 0,2074 | 0,109719145 |
| 91,5 | 0,2074 | 0,109719145 |
| 92 | 0,2074 | 0,109719145 |
| 92,5 | 0,2074 | 0,109719145 |
| 93 | 0,2074 | 0,109719145 |
| 93,5 | 0,2074 | 0,109719145 |
| 94 | 0,2074 | 0,109719145 |
| 94,5 | 0,2074 | 0,109719145 |
| 95 | 0,35634 | 0,197715761 |
| 95,5 | 0,35634 | 0,197715761 |
| 96 | 0,35634 | 0,197715761 |
| 96,5 | 0,35634 | 0,197715761 |
| 97 | 0,35634 | 0,197715761 |
| 97,5 | 0,35634 | 0,197715761 |
| 98 | 0,35634 | 0,197715761 |
| 98,5 | 0,35634 | 0,197715761 |
| 99 | 0,5 | 0,292893219 |
| 99,5 | 0,5 | 0,292893219 |
| 100 | 0,5 | 0,292893219 |
| 100,5 | 0,5 | 0,292893219 |
| 101 | 0,5 | 0,292893219 |
| 101,5 | 0,5 | 0,292893219 |
| 102 | 0,5 | 0,292893219 |
| 102,5 | 0,5 | 0,292893219 |
| 103 | 0,5 | 0,292893219 |
| 103,5 | 0,5 | 0,292893219 |
| 104 | 0,5 | 0,292893219 |
| 104,5 | 0,5 | 0,292893219 |
| 105 | 0,5 | 0,292893219 |
| 105,5 | 0,5 | 0,292893219 |
| 106 | 0,5 | 0,292893219 |
| 106,5 | 0,5 | 0,292893219 |
| 107 | 0,5 | 0,292893219 |
| 107,5 | 0,5 | 0,292893219 |
| 108 | 0,5 | 0,292893219 |
| 108,5 | 0,5 | 0,292893219 |
| 109 | 0,5 | 0,292893219 |
| 109,5 | 0,5 | 0,292893219 |
| 110 | 0,5 | 0,292893219 |
| 110,5 | 0,5 | 0,292893219 |
| 111 | 0,5 | 0,292893219 |
| 111,5 | 0,5 | 0,292893219 |
| 112 | 0,5 | 0,292893219 |
| 112,5 | 0,5 | 0,292893219 |
| 113 | 0,5 | 0,292893219 |
| 113,5 | 0,5 | 0,292893219 |
| 114 | 0,5 | 0,292893219 |
| 114,5 | 0,5 | 0,292893219 |
| 115 | 0,5 | 0,292893219 |
| 115,5 | 0,5 | 0,292893219 |
| 116 | 0,5 | 0,292893219 |

## Appendix 2

Half year mortality of lung cancer per stage

| AGE | Mortality stage I-II | Mortality stage III | Mortality stage IV |
|---|---|---|---|
| 40 | 0 | 0 | 0 |
| 40,5 | 0,088956642 | 0,251668523 | 0,530958424 |
| 41 | 0,088956642 | 0,251668523 | 0,530958424 |
| 41,5 | 0,163339973 | 0,408392022 | 0,7 |
| 42 | 0,163339973 | 0,408392022 | 0,7 |
| 42,5 | 0,212599213 | 0,490098049 | 0,776393202 |
| 43 | 0,212599213 | 0,490098049 | 0,776393202 |
| 43,5 | 0,251668523 | 0,530958424 | 0,8 |
| 44 | 0,251668523 | 0,530958424 | 0,8 |
| 44,5 | 0,278889745 | 0,564110106 | 0,826794919 |
| 45 | 0,278889745 | 0,564110106 | 0,826794919 |
| 45,5 | 0,307179677 | 0,587689437 | 0,826794919 |
| 46 | 0,307179677 | 0,587689437 | 0,826794919 |
| 46,5 | 0,336675042 | 0,612701665 | 0,858578644 |
| 47 | 0,336675042 | 0,612701665 | 0,858578644 |
| 47,5 | 0,359687576 | 0,625834261 | 0,858578644 |
| 48 | 0,359687576 | 0,625834261 | 0,858578644 |
| 48,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 49 | 0,3755002 | 0,639444872 | 0,858578644 |
| 49,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 50 | 0,3755002 | 0,639444872 | 0,858578644 |
| 50,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 51 | 0,3755002 | 0,639444872 | 0,858578644 |
| 51,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 52 | 0,3755002 | 0,639444872 | 0,858578644 |
| 52,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 53 | 0,3755002 | 0,639444872 | 0,858578644 |
| 53,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 54 | 0,3755002 | 0,639444872 | 0,858578644 |
| 54,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 55 | 0,3755002 | 0,639444872 | 0,858578644 |
| 55,5 | 0,3755002 | 0,639444872 | 0,858578644 |

| | | | |
|---|---|---|---|
| 56 | 0,3755002 | 0,639444872 | 0,858578644 |
| 56,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 57 | 0,3755002 | 0,639444872 | 0,858578644 |
| 57,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 58 | 0,3755002 | 0,639444872 | 0,858578644 |
| 58,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 59 | 0,3755002 | 0,639444872 | 0,858578644 |
| 59,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 60 | 0,3755002 | 0,639444872 | 0,858578644 |
| 60,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 61 | 0,3755002 | 0,639444872 | 0,858578644 |
| 61,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 62 | 0,3755002 | 0,639444872 | 0,858578644 |
| 62,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 63 | 0,3755002 | 0,639444872 | 0,858578644 |
| 63,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 64 | 0,3755002 | 0,639444872 | 0,858578644 |
| 64,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 65 | 0,3755002 | 0,639444872 | 0,858578644 |
| 65,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 66 | 0,3755002 | 0,639444872 | 0,858578644 |
| 66,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 67 | 0,3755002 | 0,639444872 | 0,858578644 |
| 67,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 68 | 0,3755002 | 0,639444872 | 0,858578644 |
| 68,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 69 | 0,3755002 | 0,639444872 | 0,858578644 |
| 69,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 70 | 0,3755002 | 0,639444872 | 0,858578644 |
| 70,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 71 | 0,3755002 | 0,639444872 | 0,858578644 |
| 71,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 72 | 0,3755002 | 0,639444872 | 0,858578644 |
| 72,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 73 | 0,3755002 | 0,639444872 | 0,858578644 |
| 73,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 74 | 0,3755002 | 0,639444872 | 0,858578644 |
| 74,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 75 | 0,3755002 | 0,639444872 | 0,858578644 |
| 75,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 76 | 0,3755002 | 0,639444872 | 0,858578644 |
| 76,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 77 | 0,3755002 | 0,639444872 | 0,858578644 |
| 77,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 78 | 0,3755002 | 0,639444872 | 0,858578644 |
| 78,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 79 | 0,3755002 | 0,639444872 | 0,858578644 |
| 79,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 80 | 0,3755002 | 0,639444872 | 0,858578644 |
| 80,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 81 | 0,3755002 | 0,639444872 | 0,858578644 |
| 81,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 82 | 0,3755002 | 0,639444872 | 0,858578644 |
| 82,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 83 | 0,3755002 | 0,639444872 | 0,858578644 |

| | | | |
|---|---|---|---|
| 83,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 84 | 0,3755002 | 0,639444872 | 0,858578644 |
| 84,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 85 | 0,3755002 | 0,639444872 | 0,858578644 |
| 85,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 86 | 0,3755002 | 0,639444872 | 0,858578644 |
| 86,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 87 | 0,3755002 | 0,639444872 | 0,858578644 |
| 87,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 88 | 0,3755002 | 0,639444872 | 0,858578644 |
| 88,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 89 | 0,3755002 | 0,639444872 | 0,858578644 |
| 89,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 90 | 0,3755002 | 0,639444872 | 0,858578644 |
| 90,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 91 | 0,3755002 | 0,639444872 | 0,858578644 |
| 91,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 92 | 0,3755002 | 0,639444872 | 0,858578644 |
| 92,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 93 | 0,3755002 | 0,639444872 | 0,858578644 |
| 93,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 94 | 0,3755002 | 0,639444872 | 0,858578644 |
| 94,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 95 | 0,3755002 | 0,639444872 | 0,858578644 |
| 95,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 96 | 0,3755002 | 0,639444872 | 0,858578644 |
| 96,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 97 | 0,3755002 | 0,639444872 | 0,858578644 |
| 97,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 98 | 0,3755002 | 0,639444872 | 0,858578644 |
| 98,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 99 | 0,3755002 | 0,639444872 | 0,858578644 |
| 99,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 100 | 0,3755002 | 0,639444872 | 0,858578644 |
| 100,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 101 | 0,3755002 | 0,639444872 | 0,858578644 |
| 101,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 102 | 0,3755002 | 0,639444872 | 0,858578644 |
| 102,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 103 | 0,3755002 | 0,639444872 | 0,858578644 |
| 103,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 104 | 0,3755002 | 0,639444872 | 0,858578644 |
| 104,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 105 | 0,3755002 | 0,639444872 | 0,858578644 |
| 105,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 106 | 0,3755002 | 0,639444872 | 0,858578644 |
| 106,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 107 | 0,3755002 | 0,639444872 | 0,858578644 |
| 107,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 108 | 0,3755002 | 0,639444872 | 0,858578644 |
| 108,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 109 | 0,3755002 | 0,639444872 | 0,858578644 |
| 109,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 110 | 0,3755002 | 0,639444872 | 0,858578644 |
| 110,5 | 0,3755002 | 0,639444872 | 0,858578644 |

| | | | |
|---|---|---|---|
| 111 | 0,3755002 | 0,639444872 | 0,858578644 |
| 111,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 112 | 0,3755002 | 0,639444872 | 0,858578644 |
| 112,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 113 | 0,3755002 | 0,639444872 | 0,858578644 |
| 113,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 114 | 0,3755002 | 0,639444872 | 0,858578644 |
| 114,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 115 | 0,3755002 | 0,639444872 | 0,858578644 |
| 115,5 | 0,3755002 | 0,639444872 | 0,858578644 |
| 116 | 0,3755002 | 0,639444872 | 0,858578644 |

## Appendix 3

1- One-way sensitivity analysis data:

Formula used to calculate lower and upper value:

x ± 1,96 * SE

| **Transition probabilities** | **Value** | **SE** | **Lower value/ Upper value*** | **Optimistic scenario** | | | | **Pessimistic scenario** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Inc. Costs | inc. QALYs | ICER | | Inc. Costs | inc. QALYs | ICER |
| **Base case results:** | | | | € 10.519,92 | 0,156 | € 67.367,31 | | € 10.584,14 | 0,015 | € 688.388,14 |
| *Strategy independent value* | | | | | | | | | | |
| No lung cancer - Lung cancer detected | 0,00075 | 0,00015 | 0,000456 | € 10.644,67 | 0,096 | € 110.676,06 | | € 10.684,40 | 0,009 | € 1.127.116,49 |
| | | | 0,001044* | € 10.397,44 | 0,215 | € 48.452,86 | | € 10.485,30 | 0,021 | € 496.769,79 |
| Stage I-II - No lung cancer | 0,337 | 0,0674 | 0,205 | € 10.542,07 | 0,113 | € 93.075,00 | | € 10.580,72 | 0,011 | € 920.080,98 |
| | | | 0,469* | € 10.502,99 | 0,189 | € 55.646,18 | | € 10.586,72 | 0,018 | € 578.066,29 |
| Stage I-II - Stage III | 0,261 | 0,1 | 0,065 | € 10.518,48 | 0,196 | € 53.669,10 | | € 10.589,11 | 0,019 | € 558.248,19 |
| | | | 0,457* | € 10.520,91 | 0,130 | € 80.978,50 | | € 10.580,86 | 0,013 | € 813.590,18 |
| Stage III - Stage IV | 0,318 | 0,1 | 0,122 | € 10.520,04 | 0,156 | € 67.368,38 | | € 10.576,09 | 0,016 | € 673.817,27 |
| | | | 0,514* | € 10.519,86 | 0,156 | € 67.366,83 | | € 10.589,41 | 0,015 | € 698.317,48 |
| *Current model transition probabilities* | | | | | | | | | | |
| Lung cancer detected - Stage I-II | 0,25 | 0,05 | 0,152 | € 10.496,94 | 0,184 | € 57.146,45 | | € 10.561,16 | 0,043 | € 246.166,48 |
| | | | 0,348* | € 10.542,94 | 0,129 | € 81.987,81 | | € 10.601,07 | -0,017 | -€ 621.799,53 |
| Lung cancer detected - Stage III | 0,25 | 0,05 | 0,152 | € 10.517,24 | 0,143 | € 73.582,05 | | € 10.581,45 | 0,012 | € 900.423,32 |
| | | | 0,348* | € 10.522,61 | 0,169 | € 62.126,43 | | € 10.586,82 | 0,029 | € 370.276,82 |
| Lung cancer detected - Stage IV | 0,5 | 0,1 | 0,304 | € 10.571,33 | 0,127 | € 82.921,62 | | € 10.635,55 | -0,013 | -€ 799.866,89 |
| | | | 0,696* | € 10.468,60 | 0,185 | € 56.651,75 | | € 10.532,82 | 0,044 | € 239.348,54 |

| *Optimistic model transition probabilities* | **Value** | **SE** | **Lower value/ Upper value*** | **Optimistic scenario** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Inc. Costs | inc. QALYs | ICER | | | | |
| **Base case results:** | | | | € 10.519,92 | 0,156 | € 67.367,31 | | | | |
| Lung cancer detected - Stage I-II | 0,8 | 0,16 | 0,4864 | € 10.565,38 | 0,069 | € 152.703,15 | | | | |
| | | | 1* | € 10.490,80 | 0,212 | € 49.525,94 | | | | |
| Lung cancer detected - Stage III | 0,1 | 0,02 | 0,0608 | € 10.522,60 | 0,161 | € 65.200,57 | | | | |
| | | | 0,1392* | € 10.517,25 | 0,151 | € 69.683,57 | | | | |
| Lung cancer detected - Stage IV | 0,1 | 0,02 | 0,0608 | € 10.511,55 | 0,162 | € 64.956,68 | | | | |
| | | | 0,1392* | € 10.528,30 | 0,150 | € 69.958,70 | | | | |
| F+ rate | 0,02 | 0,004 | 0,01216 | € 10.218,59 | 0,156 | € 65.437,63 | | | | |
| | | | 0,02784* | € 10.816,75 | 0,156 | € 69.268,11 | | | | |
| False + - Stage I-II | 0,8 | 0,16 | 0,4864 | € 10.520,81 | 0,154 | € 68.111,08 | | | | |
| | | | 1* | € 10.519,36 | 0,157 | € 66.901,29 | | | | |
| False + - Stage III | 0,1 | 0,02 | 0,0608 | € 10.519,98 | 0,156 | € 67.323,89 | | | | |
| | | | 0,1392* | € 10.519,87 | 0,156 | € 67.410,78 | | | | |
| False + - Stage IV | 0,1 | 0,02 | 0,0608 | € 10.519,76 | 0,156 | € 67.318,82 | | | | |
| | | | 0,1392* | € 10.520,09 | 0,156 | € 67.415,86 | | | | |
| | | | | | | | | | | |
| *Pessimistic model transition probabilities* | | | | | | | | **Pessimistic scenario** | | |
| **Base case results:** | | | | | | | | € 10.584,14 | 0,015 | € 688.388,14 |
| Lung cancer detected - Stage I-II | 0,3 | 0,06 | 0,1824 | | | | | € 10.607,15 | -0,012 | -€ 870.086,94 |
| | | | 0,4176* | | | | | € 10.567,17 | 0,048 | € 220.823,38 |
| Lung cancer detected - Stage III | 0,4 | 0,08 | 0,2432 | | | | | € 10.594,86 | 0,036 | € 293.051,56 |
| | | | 0,5568* | | | | | € 10.573,43 | -0,064 | -€ 165.196,20 |
| Lung cancer detected - Stage IV | 0,3 | 0,06 | 0,1824 | | | | | € 10.559,14 | 0,032 | € 327.330,13 |
| | | | 0,4176* | | | | | € 10.609,11 | -0,103 | -€ 102.677,11 |
| F+ rate | 0,02 | 0,004 | 0,01216 | | | | | € 10.284,03 | 0,015 | € 668.869,11 |
| | | | 0,02784* | | | | | € 10.879,76 | 0,015 | € 707.615,18 |
| False + - Stage I-II | 0,3 | 0,06 | 0,1824 | | | | | € 10.584,47 | 0,015 | € 717.826,66 |
| | | | 0,4176* | | | | | € 10.583,81 | 0,016 | € 661.266,63 |
| False + - Stage III | 0,4 | 0,08 | 0,2432 | | | | | € 10.584,35 | 0,016 | € 670.814,95 |
| | | | 0,5568* | | | | | € 10.583,93 | 0,015 | € 706.907,18 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| False + - Stage IV | 0,3 | 0,06 | 0,1824 | | | | | € 10.583,65 | 0,016 | € 673.987,75 |
| | | | 0,4176* | | | | | € 10.584,63 | 0,015 | € 703.415,64 |
| | | | | | | | | | | |
| *Costs* | | | | | | | | | | |
| *Direct costs* | | | | | | | | | | |
| Stage I-II | 16.077 | 221 | 15643,94 | € 10.516,18 | 0,156 | € 67.343,31 | | € 10.583,80 | 0,0154 | € 688.366,07 |
| | | | 16510,26* | € 10.523,67 | 0,156 | € 67.391,30 | | € 10.584,48 | 0,0154 | € 688.410,21 |
| Stage III | 16.077 | 221 | 15643,28 | € 10.519,92 | 0,156 | € 67.367,28 | | € 10.583,01 | 0,0154 | € 688.314,65 |
| | | | 16510,91* | € 10.519,93 | 0,156 | € 67.367,34 | | € 10.585,27 | 0,0154 | € 688.461,62 |
| Stage IV | 33.456 | 325 | 32819,23 | € 10.524,35 | 0,156 | € 67.395,66 | | € 10.585,74 | 0,0154 | € 688.492,46 |
| | | | 34093,10* | € 10.515,50 | 0,156 | € 67.338,96 | | € 10.582,54 | 0,0154 | € 688.283,82 |
| *Indirect costs- before retirement* | | | | | | | | | | |
| Stage I-II | 3.858 | 772 | 2345,67 | € 10.509,23 | 0,156 | € 67.298,84 | | € 10.583,17 | 0,0154 | € 688.325,09 |
| | | | 5370,36* | € 10.530,61 | 0,156 | € 67.435,78 | | € 10.585,11 | 0,0154 | € 688.451,19 |
| Stage III | 6.105,31 | 1.221 | 11602,74 | € 10.519,90 | 0,156 | € 67.367,18 | | € 10.579,04 | 0,0154 | € 688.056,21 |
| | | | 16389,30* | € 10.519,94 | 0,156 | € 67.367,43 | | € 10.589,24 | 0,0154 | € 688.720,07 |
| Stage IV | 13.996 | 2.799 | 8509,58 | € 10.551,03 | 0,156 | € 67.566,50 | | € 10.595,40 | 0,0154 | € 689.120,19 |
| | | | 19482,46* | € 10.488,82 | 0,156 | € 67.168,11 | | € 10.572,88 | 0,0154 | € 687.656,08 |
| Indirect costs- After retirement | | | | | | | | | | |
| Stage I-II | 2.679 | 536 | 1628,94 | € 10.518,26 | 0,156 | € 67.356,67 | | € 10.583,99 | 0,0154 | € 688.378,41 |
| | | | 3729,41* | € 10.521,58 | 0,156 | € 67.377,94 | | € 10.584,29 | 0,0154 | € 688.397,87 |
| Stage III | 3.728,34 | 746 | 2266,83 | € 10.519,92 | 0,156 | € 67.367,29 | | € 10.583,45 | 0,0154 | € 688.343,27 |
| | | | 5189,85* | € 10.519,93 | 0,156 | € 67.367,33 | | € 10.584,83 | 0,0154 | € 688.433,00 |
| Stage IV | 9.991,19 | 1.998 | 6074,64 | € 10.524,94 | 0,156 | € 67.399,43 | | € 10.585,97 | 0,0154 | € 688.507,00 |
| | | | 13907,73* | € 10.514,91 | 0,156 | € 67.335,18 | | € 10.582,31 | 0,0154 | € 688.269,27 |
| | | | | | | | | | | |
| *Monitoring costs* | | | | | | | | | | |
| Baseline costs (first year) | 800 | 160 | 486,40 | € 10.363,20 | 0,156 | € 66.363,67 | | € 10.427,41 | 0,0154 | € 678.194,78 |
| | | | 1113,60* | € 10.676,65 | 0,156 | € 68.370,94 | | € 10.740,87 | 0,0154 | € 698.581,50 |
| Costs after the first year | 500 | 100 | 304 | € 6.797,45 | 0,156 | € 43.529,40 | | € 6.877,72 | 0,0154 | € 447.324,37 |
| | | | 696* | € 14.242,39 | 0,156 | € 91.205,21 | | € 14.290,56 | 0,0154 | € 929.451,91 |
| False + (diagnose costs) | 2025 | 52 | 1923,67 | € 10.141,97 | 0,156 | € 64.946,96 | | € 10.207,72 | 0,0154 | € 663.905,84 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2126,33* | € 10.897,88 | 0,156 | € 69.787,65 | | € 10.960,56 | 0,0154 | € 712.870,43 |
| *Utility* | | | | | | | | | | |
| No lung cancer | 0,89 | 0,05 | 0,792 | € 10.519,92 | 0,197 | € 53.313,45 | | € 10.584,14 | 0,0714 | € 148.147,30 |
| | | | 1* | € 10.519,92 | 0,115 | € 91.482,96 | | € 10.584,14 | -0,0407 | -€ 260.098,25 |
| Stage I-II | 0,76 | 0,152 | 0,462 | € 10.519,92 | 0,152 | € 69.093,07 | | € 10.584,14 | 0,0150 | € 704.556,73 |
| | | | 1* | € 10.519,92 | 0,159 | € 66.038,52 | | € 10.584,14 | 0,0157 | € 675.892,87 |
| Stage III | 0,7 | 0,14 | 0,426 | € 10.519,92 | 0,156 | € 67.369,62 | | € 10.584,14 | 0,0143 | € 740.368,87 |
| | | | 0,974* | € 10.519,92 | 0,156 | € 67.365,00 | | € 10.584,14 | 0,0165 | € 643.227,62 |
| Stage IV | 0,53 | 0,106 | 0,322 | € 10.519,92 | 0,158 | € 66.434,74 | | € 10.203,48 | 0,0163 | € 627.210,13 |
| | | | 0,738* | € 10.519,92 | 0,154 | € 68.326,43 | | € 10.203,48 | 0,0147 | € 695.185,61 |
| False + | 0,89 | 0,178 | 0,541 | € 10.519,92 | 0,114 | € 92.040,60 | | € 10.203,48 | 0,0139 | € 733.095,10 |
| | | | 1* | € 10.519,92 | 0,214 | € 49.150,33 | | € 10.203,48 | 0,0160 | € 639.204,96 |
| | | | | | | | | | | |