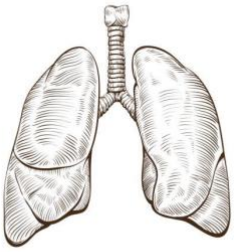
M.Sc.

Business Administration and Innovation in Health Care

Master's Thesis (CIHCO4000E)

Economic Evaluation of a Lung Cancer Screening Program in Denmark



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Abstract

Background: Around the world, cancer is a leading cause of death, and in Denmark, lung cancer is the most deadly type of cancer. Early detection can increase survivability. As the early stages of lung cancer are often asymptomatic, a lung cancer screening program could be a means for early detection. Several randomized clinical trials have been conducted to evaluate the effectiveness of the lung cancer screening program. However, there is no study conducted in Denmark evaluating the program's cost-effectiveness.

Objective: Conduct a cost-utility analysis to determine the cost-effectiveness of a low-dose computed tomography lung cancer screening program for a specified risk group, applying Danish costs.

Methods: A cost-utility analysis is conducted using Danish costs from a healthcare payer perspective, and quality-adjusted life-years gathered through the standard gamble method. The cohort includes heavy former or current smokers with a ≥30 smoking history between ages 55 and 74. The output was illustrated through a decision tree and created two cohort Markov models, with 15 one-year cycles. The first Markov model included the current standard clinical diagnosis pathway, and the second one included diagnosis through an annual low-dose computed tomography lung cancer screening program. The output is measured as costs, quality-adjusted life-years, and total diagnosed and dead. Data and parameters used in the Markov model were gathered from current literature and research. Deterministic sensitivity analysis was conducted.

Results: The base case result is cost-effective and expressed through the incremental cost-effectiveness ratio of 721,101 DKK/quality-adjusted life-years below the Swedish threshold of 881,316 DKK/quality-adjusted life-years. The epidemiological results showed more individuals diagnosed and fewer dead patients in the screening cohort versus the current clinical pathway cohort. The deterministic sensitivity analysis showed robustness against several parameters but not all.

Conclusion: Introducing a low-dose computed tomography lung cancer screening program in Denmark could be effective for the defined risk group but more costly than the current clinical care.

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1. Introduction

Healthcare costs are rising worldwide, and at the same time, patients' expectations are increasing (Topol, 2015). Health service managers face challenges in delivering and implementing innovations for healthcare because of shrinking budgets and complex systems with several stakeholder views and agendas to consider (Davey et al., 2011). This predicament leads to a growing need to evaluate and demonstrate *value* for healthcare (Davey et al., 2011).

Value in health care is the measured improvement in a patient's health outcomes for the cost of achieving that improvement (Porter, 2022). A paradox has formed where healthcare costs rise, services are restricted, standards of care lag behind benchmarks and best practices are slow to spread (Porter, 2022). As a result, patients cannot see value in the care they receive. Addressing these issues can be achieved through introducing innovations to improve efficiencies and benefits in the delivery and consumption of healthcare. Discovering the relevance and potential benefits of innovations can be challenging due to the overwhelming volume produced (Singhal et al., 2021). Decision-makers require guidance to maximize the benefits of their resource allocation and ensure these benefits are felt downstream by patients.

Decision-makers in a Beveridge healthcare system have to allocate a health budget and choose between different diseases, healthcare innovations, and interventions. There are different approaches to clarifying problems and guiding decision-makers. These can, for example, be through a Health Technology Assessment (HTA), a quality-assurance project, clinical guidelines, traditional expert opinions, stakeholder-based committee work, systematic literature reviews, economic analysis, and so on (Kristensen & Sigmund, 2008). Around the world, larger economies are requesting HTAs which is becoming a common method to evaluate health technologies (Mudili, 2022).

The European Council states that "Health technology assessment (HTA) is a scientific evidence-based process that allows competent authorities to determine the relative effectiveness of new or existing health technologies" (The European Parliament and the Council of the European Union, 2021). They acknowledge the added value of health technology articulated through HTA and how it acts as a vehicle for comparing technologies. Shortly, one can say that a HTA is preferred when making decisions regarding the use of technology at all healthcare system levels. Economic evaluations (EE) are, according to Chen (2022), one of the backbones of HTA, assessing the cost-effectiveness of health technology. It balances the costs and health benefits of new health technologies and aims to meet the needs of the decision-makers. Furthermore, within the EE, the decision-analytic methodology framework meets all the needed requirements for a decision-making context (Sculpher et al., 2006).

The relevance of EEs has emerged out of the difficulties in allocating resources between different interventions and how resources are best utilized (Drummond et al., 2015). The goal is for using health care resources efficiently so the most health benefits are achieved. The EE is a framework that can evaluate and organize clinical evidence to consider the effects and costs of alternative interventions (Drummond et al., 2015). There are several methods for EE; the most common is cost-utility analysis (CUA). Since EEs can evaluate any health technology, identifying relevant areas has to be a step in the evaluation process. One way to identify areas or diseases which would benefit from innovative and cost-effective technologies is to identify the most common deadly diseases worldwide.

The World Health Organization (WHO, 2020) identified cancer as a leading cause of death worldwide. In 2020 there were nearly 10 million cancer deaths worldwide, of which lung cancer was the most deadly cancer type, accounting for 1.8 million deaths with a current 5-year survival rate of <20% (World Health Organization, 2020). To reduce the cancer incidence burden, the WHO (2022) states that 30 to 50% of cancers can be prevented by avoiding risk factors and implementing evidence-based prevention strategies. Furthermore, early detection and appropriate treatment can reduce cancer mortality. Together, this leads to identifying the problem statement and the following section.

1.1 Problem Statement and Motivation

To reduce lung cancer mortality, the WHO explains two main approches: early diagnosis and screening. Early diagnosis requires the disease to have symptoms and the patients or clinicians to be aware of those symptoms. This method is not preferred for diagnosing lung cancer in early stages, as these patients are often asymptomatic or with mild or ambiguous lung cancer symptoms (Yang et al., 2019). At the same time the patient's prognosis worsens when lung cancer is diagnosed in later, more symptomatic stages (Snowsill et al., 2018). Late-stage detection leads to advanced diagnoses and limits treatment options. The American Lung Association (2020) reports that the current 5-year prognosis for all- stage lung cancer has an 80% mortality rate. Table 1 below illustrates survivability estimates in different lung cancer stages and these numbers illustrate the relevance of screening programs (Snowsill et al., 2018).

Screening is a pathway to early-stage lung cancer identification, diagnosis, staging, and treatment without placing responsibility on the patients or clinicians to identify ambiguous symptoms of the disease, currently being an issue (Woodard et al., 2016). Screening is said to lower lung cancer mortality or improve oncological outcomes (EUnetHTA, 2020). This could be due to the early diagnosis since for instance stage I patients have an 82% *survival rate* over 5-years with surgery compared to stage IV with 17%, clearly presenting the relevance.

Table 1. Lung Cancer Survivability

Lung Cancer Survivability		
Stage	2-year survival	5-year survival
Stage I	93%	82%
Stage II	79%	65%
Stage III	47%	26%
Stage IV	17%	5%

Note. American Lung Association, 2020

Despite the relevance of early diagnosis of lung cancer, no European country is yet to implement a screening program in 2022, even though technologies are readily available. Denmark has the third highest mortality rate for lung cancer in Europe (OECD, n.d.). Between 2005 and 2007, the one-year relative survival for all stages of lung cancer in Denmark was 35% compared to Sweden at 44% (Coleman et al., 2011). Guldbrandt et al. (2015) explain that a late-stage detection and diagnosis could explain this, along with increased waiting time and diagnostic delay. It could also be explained by lung cancer awareness among patients or by the correlation between lung cancer and smoking (European Respiratory Society, n.d.). In 2020 there were 21% of men, and 15% of women smoked amongst the Danish population (Statista, 2021b).

Even though Denmark has a high lung cancer death rate, despite the large smoking population, and other screening programs for cancer in place, there is no LCSP in 2022. Previous studies in Denmark have identified the increased cost when introducing a LCSP in Denmark (Rasmussen et al., 2014) but have not put the cost in relation to the health benefits. There is presently no EE conducted on screening tools for lung cancer in Denmark, which makes it difficult for decision-makers to decide whether to consider a LCSP.

Based on these facts, this thesis will identify potential new value-based screening innovations that have currently not been used to detect all stages of lung cancer. It will attempt to follow the HTA and EE methodology to guide decision-makers on evidence-based foundations to assess relevant evidence regarding the consequences and circumstances in the evaluation of the innovation. The following section will further explain the objective of the thesis and present the research question.

1.2 Objective and Research Question

This thesis aims to conduct a CUA to determine if a LCSP should be considered in Denmark, primarily by assessing the cost-effectiveness of a screening innovation. Being the most common EE, the CUA will be

conducted using the current treatment costs for lung cancer in Denmark. The potential costs for introducing a LDCT screening program will be added to the treatment costs to evaluate the chosen screening innovation. Furthermore, the health benefits or outcomes will be measured in quality-adjusted life-year (QALY) taken from the literature, as Denmark does not have QALY data on LCSP or lung cancer in general as of 2022. The objective is therefore mainly to conduct an EE but other epidemiological results on diagnosis rate and mortality will also be sought after, as well as an analysis of the feasibility of introducing a LCSP in the Danish context. This thesis therefore aims to answer the following research question:

Why should the Danish Ministry of Health consider a lung cancer screening program for detecting lung cancer among a heavy-smoking population aged 55-74 years?

1.3 Delimitation

This project's scope was determined with the researcher's supervisor, Benjamin Serena, to create a realistic research goal within the limited time frame, which fulfilled the academic requirements set by Copenhagen Business School and the academic goals set by the researchers. There are several delimitations within this thesis:

1. The thesis is limited to only exploring screening programs for lung cancer within a Danish setting.
2. The only screening program technique that is evaluated with the comparator is a low-dose computed tomography (LDCT).
3. The study focuses on the pre-diagnostic disease progression of non-small cell lung cancer (NSCLC), then its treatment, mortality, and associated costs.
4. The choice of EE is a CUA and does not include post-diagnosis disease progression, aftercare or palliative care.

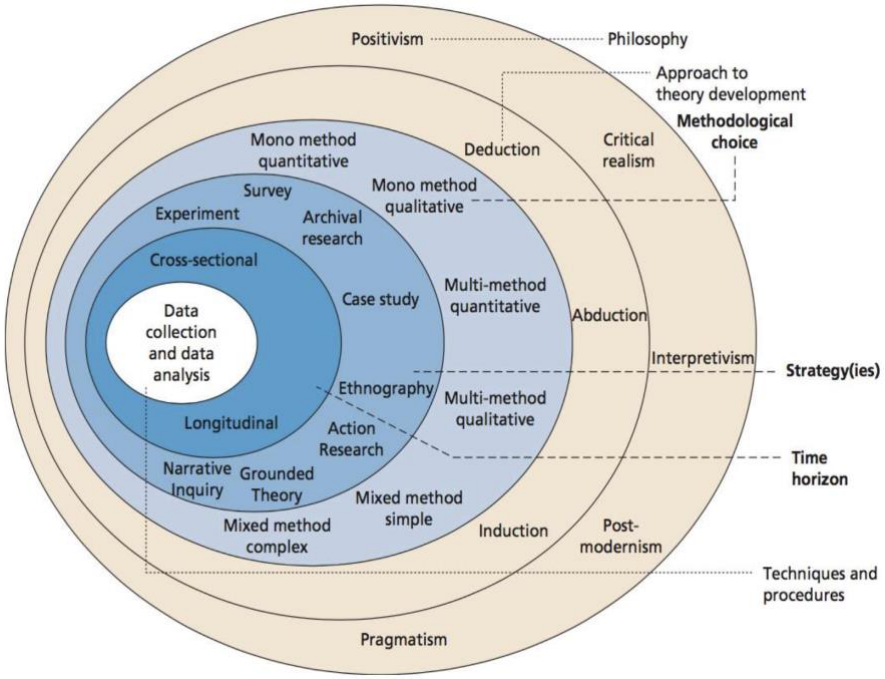
Another delimitation within this study is the absence of empirical research or data collection. The researchers could not conduct clinical trials within the field of lung cancer screening due to limited resources. Therefore, all data for this thesis was obtained through literature searches from randomized control trials (RCT) and experts within the field. Furthermore, the methodological choices were guided by the available and applicable data obtained during the research process. The only primary data obtained was via informal interviews with experts within cancer and epidemiology, used to reinforce choices made within the model. Having outlined the boundaries for the thesis, the following section will describe the methodological decisions when writing the thesis.

1.4 Philosophy of Science

The methodology for answering the research question should be structured and organized (Saunders et al., 2022). Saunders et al. (2022) present a model that aims to explain the different stages of writing a thesis in an

organized way. Illustrated in Figure 1 is one of many models that can be used to understand various methodological decisions. The research onion effectively ensures that the method used matches the aim of the research (Saunders et al., 2022). It allows the researchers to draw valid and trustworthy conclusions. The model consists of six layers, the first being the Philosophy of Science.

Figure 1. Research Onion



Note: Saunders et al., 2022

The philosophy of science refers to the researcher's perceptions, understandings, or worldviews from which the research is conducted and is usually studied in terms of epistemology and ontology (Kragh, 2007). Epistemology refers to the valid information required and how to obtain this information for the research conducted. At the same time, ontology refers to the authenticity of this information and understanding it. There are five main philosophical approaches for business and management according to Saundlers et al. (2022); *positivism, realism, interpretivism, post-modernism,* and *pragmatism.*

This thesis will employ a pragmatism stance since it is suitable for the objective and nature of the research question. This study aims to create a model and gather data on cost and health effects that can be used in the created economic model to arrive at a conclusion where decision-makers can be guided in their choices on allocating the healthcare budget between interventions. This goes in line with the pragmatist's research that starts with a problem and aims to formulate practical solutions to inform future practice (Saunders et al., 2022). The only relevant concepts support *action* (Keleman & Rumens, 2008). The most important determinant for

the strategy and research design for this research is to address the research problem and research question, and this is just what a pragmatist would want it to be (Saunders et al., 2022). A pragmatist would also recognize that one can interpret the world differently and that multiple methods can be used for multiple realities. However, a pragmatist does not always have to use all the multiple methods available but is the most credible, reliable, and well-founded with the most relevant data for the research (Kelemen & Rumens, 2008). This thesis will further explain the gathering of data and aim to be the most credible and relevant.

The researchers would prefer to stance from a positivism philosophy. However, this was not possible because the gathering of QALY data used in the study could not be seen as credible and meaningful since it comes from individuals' opinions gathered through the standard gamble method. The positivist promises unambiguous and accurate knowledge and data uninfluenced by human interpretation or bias. Since the QALY data is gathered based on individuals' perceptions, it was not possible to follow this philosophy. The rest of the methods were not suitable philosophies for seeking answers to the research questions.

The following layer in the research onion is the choice of the intended approach to theory development. The three different approaches to theory development are (1) the deductive, (2) inductive, and (3) the abductive approach (Saunders et al., 2022). This thesis does not aim to test a theory and does not follow the deductive approach. The inductive approach is not fully applicable either since the researchers aim to answer the research question by partly using the frameworks for EE and partly also modify these frameworks. The abductive approach is, therefore, the approach used for theory development. Data is collected to explore a phenomenon and identify themes and patterns (Saunders et al., 2022). The aim is to modify the existing models for EE to test the cost-effectiveness of cost and QALY data. The researchers will explain both the existing theories and the theory building and modifications in the *methodology* section below. The approach incorporates a process where the researchers move back and forth and combine deductive and inductive approaches (Suddaby, 2006).

1.5 Research Design

Following the third layer of the research onion (Figure 1), the methodological choice has to be made (Saunders et al., 2022). In research, there are multiple approaches to theory development distinguished both in qualitative and quantitative literature. Qualitative methods help explore phenomena, smaller groups, and their meanings (Basias & Pollalis, 2018). Quantitative research can examine larger populations, linking empirical observation with quantitative relations as mathematical expressions (Basias & Pollalis, 2018). Quantitative research is associated with experiments and survey research strategies. However, the analysis of such research is often performed qualitatively (Saunders et al., 2022). The research method is dependent on the aims of the research question. As shown in Figure 1, six different methods separate or combine the qualitative and quantitative data

differently. This thesis follows the mixed-model approach using quantitative, focusing on numerical data, while qualitative data focuses on textual, audio, and visual research (Saunders et al., 2022).

The mixed-model research approach combines various qualitative and quantitative strategies within a single project that may have qualitative or quantitative theoretical drivers (Saunders et al., 2022). The research process follows the characteristics of mixed-model research, which allows iterative collection, analysis, interpretation, and presentation of research (Saunders et al., 2022). Within this process, quantitative data can be qualified, while qualitative data can be quantitated to create understanding between the research (Saunders et al., 2022). This method can combine an overview of the disease and the associated literature, the Danish context, and HTA theory. The limitations following the mixed-model research approach could be that it is complex to conduct and requires more expertise and time in data collection and analysis. However, as the qualitative methods are not being wholly and rigorously followed and used to triangulate the data with quantitative methods, a mixed-method approach applies over a multi-method.

The fourth layer regarding strategy is connected to the objectives of the study. The research strategy will from a practical perspective dictate how the research will be conducted, and include several methods to capture all relevant literature (Saunders et al., 2022). Archival research will be used primarily to source the necessary health information required, with a secondary a grounded theory approach will also be used to help predict and explain behaviors (Saunders et al., 2022). This approach will enable the researchers to conclude commonalities between literature and the data produced from the applied framework (Saunders et al., 2022). The use of these strategies will allow for both the quantitative and qualitative research approaches to be undertaken to produce, interpret and contextualize the data. A shortcoming of a grounded theory is that it tends to produce numerous amounts of data and is difficult to manage without standard rules to identify categories (Saunders et al., 2022). The researchers will overcome these obstacles and mention the difficulties in management of data in the limitations section.

The fifth layer is about the time horizon (Saunders et al., 2022), where the researchers had to decide upon taking data from a single point in time or throughout a given period. The researchers collected data that had followed patients over multiple periods by using the longitudinal approach. The model being created for this thesis will use this data to further predict disease progression and the associated epidemiological developments in the screening cohort versus the comparator cohort over time and not just a single point of time.

The last inner layer of the research onion (Figure 1) is the *data collection and analysis* (Saunders et al., 2022). The quantitative data will be collected and simulated through a developed model, while the qualitative data will be collected through grounded theory. Multiple sources will be identified to help develop the theoretical

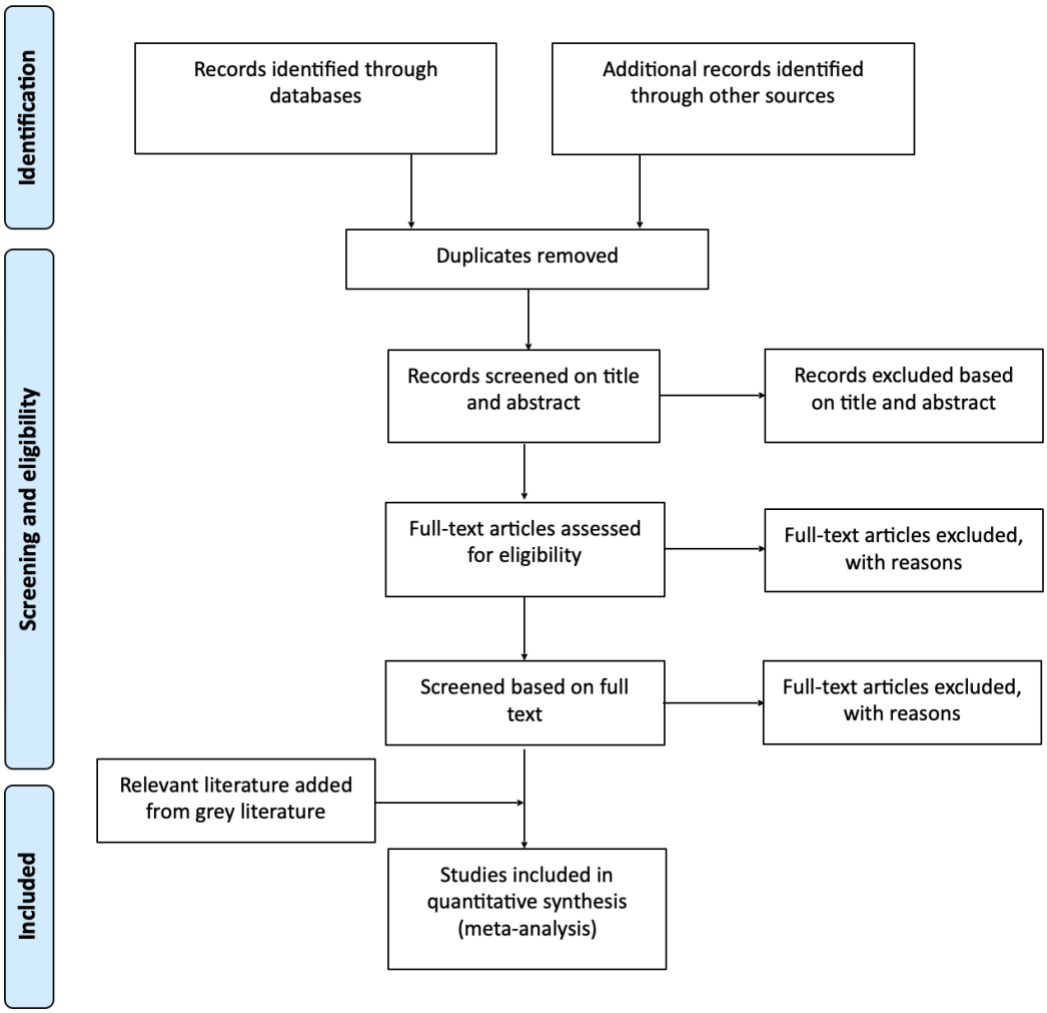
framework for the CUA to construct the EE. Recommended books will include health economics, such as *Methods for the Economic Evaluation of Health Care Programs* (Drummond et al., 2015) and *Decision Modeling for Health Economic Evaluation* (Briggs et al., 2006), relevant academic journals, and government health economics publications and websites. There are three main aspects of the research collection process for the qualitative and quantitative data in this thesis:

- Lung cancer background research
- A review of lung cancer in the Danish context
- A systematic literature review of randomized control trials (RCT) and EEs

A broad search was performed to find information on the three main aspects through literature, scholarly databases, and books connected to the thesis scope in health and economics. Due to the broad scope, multiple literature searches were performed to obtain the relevant information. The data collected for this thesis was extracted from multiple sources, including databases, governmental websites, and Ministry of Health submissions in a structured literature search, including the Snowball Method. The databases accessed focused on science, health, business, and economics, including PubMed/MEDLINE, NCIB, Scopus, Google Scholar, ScienceDirect, Mendeley, Cochrane Library, CBS Library, ResearchGate, and NHS EED. These databases were accessed continually from December 2021 until May 2022. Boolean search terms were used to limit and define search results (Ferguson & Hebels, 2003). Other documents, including gray literature, were sourced from Danish government sites, various Danish cancer societies, and health authority pages. The researchers have aimed to search, identify, evaluate, and include existing scientific knowledge published in this field by conducting a structured literature search.

Additionally, a structured literature search contributes to identifying relevant literature, which reduces the risk of biased reviews (Saunders et al., 2022). All articles were first screened by titles and abstracts to remove unwanted literature. A full-text assessment was performed to examine viability and relevance, with texts excluded if they were not within the scope, with the included literature presented throughout the thesis. The literature search methodology is visualized in Figure 2 with the literature searches articulated below.

Figure 2. Literature Search Methodology



Note. PRISMA, n.d.

Background of Lung Cancer

The background review aims to investigate lung cancer, its causes, the process of diagnosis, treatment, and mortality. Relevant literature was identified to define and articulate lung cancer as a disease and its impact on those diagnosed. The search terms utilized were *lung cancer*, epidemiology, incidence, prevalence, mortality, treatment, cost, high risk, causes, statistics,* and *demographics*.

Danish Context

To highlight the Danish context, the epidemiology of lung cancer was explored in Denmark, with the costs of lung cancer to the Danish taxpayer explained. Relevant literature about Denmark and lung cancer, lung cancer screening programs, randomized control trials, and associated economic evaluations was extracted using the

search terms *Denmark, lung cancer*, screen* epidemiology, mortality, treatment, cost, high risk,* and *non-small cell lung cancer.*

Lung Cancer Screening Randomized Control Trials and Economic Evaluations

A systematic literature review is performed on lung cancer screening trials and CUA studies assessing the economic viability of the screening program. The hierarchy of evidence referenced by Drummond et al. (2015) is used as a guiding principle to rank research designs to include the relevant literature. A study design provided high levels of internal validity. The hierarchy of evidence, as explained by Cook (1997), includes:

1. No-of-1 randomized trial
2. Systematic review of randomized trials
3. Single randomized trial
4. Systematic review of observational studies
5. Single observational study
6. Physiological study
7. Unsystematic clinical observations

Relevant literature was identified about lung cancer screening programs, randomized control trials, and associated economic evaluations were extracted using the search terms *lung cancer*, screen* epidemiology, LDCT, low dose computed tomography, diagnosis, treatment, mortality, high risk, non-small cell lung cancer, cost-effective*, cost-utility, cost-benefit, economic*, health economic evaluation, model, modelling, Markov model, QALY, quality-adjusted life-year*.*

The final step of the research onion involves analyzing the data (Saunders et al., 2022). Multiple analysis techniques will be used for the quantitative data. A descriptive approach will give an overview of the data, while an exploratory, causal, and mechanical analysis will find and determine the relationships when sensitivity testing is performed (Saunders et al., 2022). Predictive analysis will also be performed to estimate the epidemiological benefits and costs associated with the intervention. A grounded theory approach will be used for the qualitative analysis to place the data within the explored context (Saunders et al., 2022). Furthermore, the limitations section of this thesis will explore the validity and reliability of the methodological choices and subsequent outcomes.

2. Background Information

This section is divided into three main chapters. The first chapter introduces lung cancer and LCSPs. The second chapter outlines the Danish context and identifies the epidemiology of the disease and costs of lung cancer in Denmark. The third section covers RCTs and previous studies on the EE of LCSPs in other countries.

Chapter 1

2.1 Lung Cancer and Lung Cancer Screening

This section will introduce lung cancer, its symptoms, causes, health states, and disease severity. The main risk groups for developing lung cancer will be identified based on current research. Furthermore, the different tools for both detection and treatment are outlined. This section aims for the reader to understand the disease and pathways to diagnosis.

2.1.1 Lung Cancer Disease Overview

Lung cancer, or lung malignancies, is a malignant growth of cells in a person's lungs or bronchial system (Snowsill et al., 2018). The type of lung malignancies by commonality is classified as non-small cell lung carcinoma (NSCLC) (79%), small-cell carcinoma (16%), and tumors such as carcinoids (5%) (EUnetHTA, 2020).

The tumor node metastasis system (TNM) was developed by the International Association for the Study of Lung Cancer and can divide lung cancer into different stages (EUnetHTA, 2020). The TNM system provides information about the size of the tumor (T), its spread to surrounding lymph nodes (N) or distant parts of the body, and whether it has metastasized (M). Mapping cancer using the TNM system allows healthcare professionals to develop a targeted treatment plan (EUnetHTA, 2020). Once classified using the TNM system, cancer can be further segmented into stages I-IV.

> **Stage I.** A small tumor has not spread to any lymph nodes, and no evidence of bronchoscopic invasion in the main bronchus. The largest dimension of the tumor is ≤ 3cm.

> **Stage II.** Spread to bronchus, but the carina is spared. The tumor invades the visceral pleura, leading to obstructive pneumonitis or atelectasis, and involves part of the lung or entire lung. The tumor is between > 3 cm and ≤ 5 cm in size.

Stage IIIA. Tumor size >5cm and ≤ 7cm, with direct invasion of the chest wall, parietal pleura, phrenic nerve, or pericardium, with different tumors located in the same lobe as the primary tumor.

Stage IIIB. Tumor size >5cm and ≤ 7cm with direct invasion to surrounding lymph nodes, visceral pleura, and bronchus.

Stage IV. Tumors are >7 cm and affect one or more of the body's other parts: the heart, diaphragm, great vessels, mediastinum, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina. Alternatively, a separate tumor nodule arises from the primary tumor location (EUnetHTA, 2020).

Lung Cancer Symptoms

The different stages of lung cancer will affect the body differently and result in different symptoms. The following can be signs and symptoms of lung cancer; cough (8%–75%), weight loss (0%–68%), dyspnoea, or shortness of breath (3%–60%), chest pain (20%–49%), hemoptysis (6%–35%), bone pain (6%–25%), fever (0%–20%) and asthenia, or generalized weakness (0%–10%) (EUnetHTA, 2020 p. 40). Early stages of lung cancer are usually asymptomatic and often undetected, with symptoms usually appearing when the disease has advanced to the lungs and other parts of the body (Chowienczyk et al., 2020; EUnetHTA, 2020). Patients often report a lack of awareness of lung cancer symptoms due to delayed detection and initiation of treatment (Ellis & Vandermeer, 2011).

Lung Cancer Progression

Metastasis is the spread of cancer outside of the primary location (National Cancer Institute, n.d.). Lung cancer metastases are multifaceted. Cancer cells will travel away from the primary tumor through the blood or lymphatic system to areas of higher oxygen concentration, forming a new tumor in other tissues or organs (Popper, 2016). When a patient moves into a higher cancer stage, the mortality rate will increase compared to the previous stage (Popper, 2016). Limiting the spread of cancer will reduce mortality and increase survival time (Popper, 2016).

Lung Cancer Mortality

Lung cancer is the biggest killer from cancer globally, accounting for 25% of all lung cancer deaths (American Lung Association, 2020). All-stage lung cancer 5-year survivability is 26%, which varies between lung cancer staging (American Lung Association, 2020). Listed in the problem statement is the survivability per lung cancer at the stage of diagnosis (American Lung Association, 2020).

Reducing Lung Cancer Mortality

The main factors used in decreasing lung cancer mortality are early detection and smoking cessation (Schabath & Cote, 2019). Cessation of smoking in earlier years is associated with a higher increase in life years added: 10 life years are added when quitting smoking in the 30s compared to four life years when quitting in the 60s (EUnetHTA, 2020). While smoking cessation should be the priority when reducing lung cancer incidence and mortality, nicotine addiction and readily accessible cigarettes can hamper the efforts of both smokers and policymakers to reduce smoking rates (Schabath & Cote, 2019).

Detecting lung cancer early is pivotal in successfully treating lung cancer. However, most lung cancer patients are diagnosed in the advanced stages of the disease, limiting curative treatment options (Schabath & Cote, 2019). As earlier explained in the problem statement, lung cancer is often asymptomatic and therefore screening could be a way to detect lung cancer in all stages. Multiple clinical trials have proven the efficacy of screening for lung cancer using LDCT scanning and the associated increase in early-stage disease detection and decrease in overall mortality (Yang et al., 2019). Having outlined the basis of the disease, the next section will identify the different risk groups at higher risk of developing lung cancer.

2.1.2 Lung Cancer Causes

Lung cancer is often a terminal disease, with some population groups at greater risk. This section will identify the groups most likely to develop lung cancer (EUnetHTA, 2020). The main risk factor for lung cancer is tobacco smoking, but other factors such as age, gender, genetic history, environmental, or comorbidities can affect the development (Barta et al., 2019; EUnetHTA, 2020).

Smoking

The main factor for lung cancer is smoking, accounting for 80% of all female lung cancer cases and deaths and 90% among men (European Respiratory Society, n.d.). *"It is estimated that individuals who smoke are 11 times more likely to develop lung cancer than those who have never smoked"* (EUnetHTA, 2020, p. 41). The number and duration of cigarettes smoked can increase the risk of lung cancer and is defined in medical terminology by the term pack-year (Barta et al., 2019). One pack-year of smoking is defined as 20 cigarettes per day per year and is used in medicine as a benchmark term to characterize the severity and intensity of smoking history (Barta et al., 2019). The risk of developing lung cancer increases with an increase in pack-year smoking history (Barta et al., 2019). The European Respiratory Society (n.d.) gathered 13 studies reporting pack-years and found that *"cigarette consumption of <20 pack years resulted in a significant threefold increase in the risk of developing lung cancer; the increase in risk was sevenfold for 20–40 pack-years, 11-fold for 40–60 pack-years and 12-fold for >60 pack years"* (EUnetHTA, 2020 p. 41). However, the risk of being diagnosed with lung cancer 15-20 years after quitting smoking is reduced by 90% compared to

those who continue to smoke (EUnetHTA, 2020). Löfling and colleagues (2019) also state that approximately 10-15% of lung cancer patients have never smoked. Hence multiple factors can, to a lesser degree, impact a person's risk of developing lung cancer.

Age

Studies show that lung cancer mainly occurs amongst older people (Eldridge, 2022). The average age of diagnosis is 70 years, with approximately 53% of cases occurring between ages 55-74 (American Cancer Society, n.d.; De Groot et al., 2018). Furthermore, 37% of lung cancers occur above 74 years, with approximately 10% of lung cancer cases occurring <55 years of age (De Groot et al., 2018). Lung cancer incidences peak at age 80, with decreased incidences due to competing mortality from other causes (De Groot et al., 2018). As patients age, treatment success and outcome prognosis for lung cancer decrease. Hence poor survivability is seen in patients once diagnosed (Torre et al., 2015).

Gender

The overall risk of developing lung cancer for men is 1 in 15, and for women, 1 in 17 for both smokers and non-smokers (Herndon, 2021). However, women are usually two years younger when diagnosed than men, and there are more young women with lung cancer than men (Eldridge, 2022a; Eldridge, 2022b).

Genetic Factors

According to the European Network for Health Technology Assessment report (2020), several studies have presented an increased risk of lung cancer in first-degree relatives of people with lung cancer. A metastudy including 24 case-control studies showed that individuals with a family history of lung cancer had a two-threefold greater susceptibility of developing lung cancer versus those with no family history of lung cancer (Coté et al., 2012). Furthermore, several registry-based studies have concluded that a family history of lung cancer will increase the early onset (EUnetHTA, 2020).

Environmental Factors

Several environmental and occupational exposures can affect lung cancer incidences, such as carcinogens, air pollution, domestic biomass fuels, and exposure to radon (Barta et al., 2019; EUnetHTA, 2020). According to Pope III (2002), workplace exposure to carcinogens, such as asbestos and other cancer-causing particles, could significantly increase the risk of developing lung cancers. Long-term exposure to fine particle air pollution increases lung cancer mortality. With each increase in fine particulate air pollution by 10-µg/m3, lung cancer mortality increased by 8% (Pope III, 2002). The WHO recommends a concentration of 40-µg/m3, with many high-trafficked areas in Copenhagen regularly exceeding this threshold (IQAir, 2022). It is also estimated that 3-14% of lung cancer can be linked to radon exposure (EUnetHTA, 2020).

Comorbidities

Other diseases, such as chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF), can also cause an increased risk of lung cancer (EUnetHTA, 2020). COPD is caused by cigarette smoking, but evidence also shows that COPD is an independent risk factor for lung cancer, with a relative risk of 2.06 (Zhang et al., 2017; EUnetHTA, 2020). Research also shows that chronic airway disease IPF is associated with a higher risk of lung cancer. The prevalence of this disease in lung cancer patients ranges from 2.7% to 48% (Ballester et al., 2019).

2.1.3 Lung Cancer Detection

There are different ways to detect and diagnose lung cancer. This section is divided into two main components, where the first one explains the current clinical pathways for diagnosis, and the second part identifies the different screening programs for diagnosis.

2.1.3.1 Diagnosis Through Standard Clinical Care

This section will outline ways to detect lung cancer through standard current clinical care. The following examinations are regarded as basic diagnosing methods; anamnesis, clinical examination, laboratory tests, chest x-ray, spiral CT of the thorax and abdomen, bronchoscopy and abdominal sonography (Latimer & Mott, 2015; Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, 2018).

When diagnosing patients through standard clinical care, a patient's general practitioner (GP) will interpret their symptoms and risk factors and examine them physically and through image-guided examinations (Mahncke Guldbrandt et al., 2015; EUnetHTA, 2020). The health care professionals' accuracy and clinical skills are essential when evaluating patient symptoms and weighing the risk of underlying diseases versus the likelihood of symptoms caused by lung cancer. Most lung symptoms do not represent underlying lung cancer. Evidence suggests that symptoms are often experienced long before a lung cancer diagnosis (Corner et al., 2005; Hamilton et al., 2005; Mahncke Guldbrandt et al., 2015). Other factors such as medical history, family history, and other risk factors for developing lung cancer must also be considered when evaluating the symptoms and patients (EUnetHTA, 2020).

The physical examination mainly assesses the lymph nodes and thoracic organs (EUnetHTA, 2020). It includes basic laboratory tests such as electrolytes, blood count, coagulation values, and liver and kidney parameters. A chest X-ray is often ordered to examine the thoracic organs (EUnetHTA, 2020). However, the chest X-ray is inaccurate, with a false-negative of 20% before diagnosis, according to Mahncke Guldbrandt and colleagues

(2015). This examination process is usually enough to diagnose NSCLC but is not enough to classify the tumor in detail (Postmus et al., 2017). If there remains suspicion of tumors, the patient will be referred for a LDCT scan to investigate further. The most used diagnostic test for lung cancer is fiber-optic bronchoscopy which also includes the assessment of regional lymph nodes through endoscopic and endobronchial (EUnetHTA, 2020).

2.1.3.2 Diagnosis Through Screening Programs

A LCSP aims to detect and treat lung cancer at an early stage (EUnetHTA, 2020). Early detection has a significant impact on the mortality rate of lung cancer, improving the oncological outcomes and leading to a better quality of life in terms of morbidity (Ma et al., 2013). It can provide opportunities for changes in unhealthy lifestyle behaviors, reduce mental stress and anxiety, and potentially identify other conditions or diseases that require treatment (Humphrey et al., 2013).

There are two main methods for screening, including (1) *imaging technologies* such as *chest X-ray* and *LDCT* and (2) *biomarkers* (EUnetHTA, 2020). The LDCT is the recommended lung cancer screening method according to several major European, American, and Asian health organizations, including (EUnetHTA, 2020). This section will therefore present the two main methods for screening for lung cancer and further explain the LDCT screening method.

The imaging technologies use ionizing radiation to diagnose lung cancer and are only initiated if the health benefits outweigh the radiation risk (EUnetHTA, 2020). The NLST demonstrated a 20% reduction in lung cancer mortality amongst people who underwent annual screening CT relative to chest x-ray. Therefore, LDCT is the recommended screening method for high-risk patients (Tanoue et al., 2015; Allen et al., 2019). The LDCT offers highly sensitive technology, enabling the detection of lung cancers <1cm (Allen et al., 2019). LDCT reduces radiation exposure by 90% compared to standard CT scanning, offering ultra-low radiation doses without compromising image quality (Allen et al., 2019). A LDCT scanner uses x-ray images and computer processing tomography to combine images, creating cross-sectional 3D images, and is used primarily for rapidly visualizing and examining internal parts of the body (Allen et al., 2019). LDCT can also guide biopsy procedures, map for surgery, and monitor the effectiveness of treatments such as radiotherapy or chemotherapy (Allen et al., 2019).

The harms of LDCT scanning can include exposure to radiation and the risk of reaction to contrast materials when used (Allen et al., 2019). Further criticism of LDCT as a means for lung cancer screening is the high false positive detection rates within screening groups, leading to overdiagnosis. False positive screening is classified as a patient having a suspicious nodule detected which is benign, requiring either increased

surveillance or escalated diagnostic interventions (Hammer et al., 2022). In the National Lung Cancer Screening Trial in the U.S. (NLST) trial, 33% of patients were found to have received a false positive screen in their first two rounds of screening. This could result in further investigations, a marked increase in psychological distress, and additional costs (Allen et al., 2019). Section 3.1 summarizes the most extensive clinical trials on LDCT and the false positive rates.

Chest x-ray was previously recommended for lung cancer screening because of negative trial results in recent studies (EUnetHTA, 2020). A chest x-ray will produce images of significant structures, including the heart, lungs, bones, and blood vessels, and detect air, fluid, and chronic lung conditions (Bradley et al., 2019). A chest x-ray is still the first-line investigation used for suspected lung cancer due to accessibility and low cost in some countries. X-rays can detect masses >1cm yet fail to detect lung cancer in >20% of symptomatic cases (Bradley et al., 2019). Therefore the recommended imaging technology for detecting lung cancer is LDCT (EUnetHTA, 2020; Allen et al., 2019).

The second method to detect early-stage lung cancer is biomarkers (EUnetHTA, 2020). Molecular biomarkers complement routine pathological testing and explain why a cell becomes cancerous (American Lung Association, 2021). Even though the methods for biomarkers have enormous potential, they are not used in practice because much improvement is still needed for the most promising biomarkers (image-based and molecular ones). The biomarkers for lung cancer are still at an early stage and have to be developed further (EUnetHTA, 2020).

A general limitation to all LCSPs is adherence since the impact of the screening is highly dependent on the participation rates of the programs (Dressler et al., 2021). The initial barrier to low adherence is the inability to consistently and systematically identify individuals in the risk group (Moldovanu et al., 2022). The same research also shows that eligible patients are more likely to undergo screening when their GP endorses it. However, clinicians report unfamiliarity with eligibility criteria and the balance between harms and benefits for different risk groups. Clinicians have also reported negative reactions from their patients and concerns about the increased workload if they would recommend a screening (Moldovanu et al., 2022).

Individuals with extensive smoking history and low socioeconomic status (SES) are less likely to attend cancer screening programs. This group is more pessimistic about survival changes for early-stage lung cancer, and they experience stigma around smoking and fear of being judged if they attend the screening (Moldovanu et al., 2022). Educational materials about a higher risk of cancer can lead to anxiety and counterproductive behavior. Some screening programs also include smoking cessation as a mandatory part, leading to less attendance amongst smokers.

A long smoke-pack history is also often associated with lower SES in Western countries (Moldovanu et al., 2022). Low SES people face higher barriers to attending screening programs because of geographical issues (travel time and cost) and lack of insurance. Mobile CT scanners can be a way to solve this problem and make screening accessible for everyone (Moldovanu et al., 2022). Another study on lung cancer showed higher adherence to centralized screening versus decentralized screening. However, overall, the annual screening was still suboptimal (Sakoda et al., 2021). The same study also concluded that individuals aged 65 to 71 who had previously smoked were more likely to adhere. When a patient has been diagnosed with lung cancer through any of the aforementioned methods, the person will be treated according to the methods explained below.

2.1.4 Treatment

This section will outline NSCLC treatment options at different diagnostic stages. Lung cancer treatment is standardized across most western countries and is based on the TNM classification system previously described in section 2.1.1. (EUnetHTA, 2020). Collins et al. (2007) describe a multimodality approach used in lung cancer treatment across differing stages, including surgery, radiotherapy, chemotherapy, and palliative care, as described in Table 2, with the treatments explained below.

Table 2. Lung Cancer Treatment by Stage

Lung Cancer Treatment by Stage			
Stage	Primary treatment	Adjuvant therapy	Five-year survival rate
Stage I	Resection	Chemotherapy	60-70%
Stage II	Resection	Chemotherapy +/- radiotherapy	40-50%
Stage IIIA	Resection +/- preoperative chemotherapy	Chemotherapy +/- radiotherapy	15-30%
Stage IIIB	Chemotherapy with concurrent or subsequent radiotherapy	None	10-20%
Stage IV	Chemotherapy	None	10-15%

Note. Collins et al., 2007

Resection

Surgical resection is the removal of tissue or part of an organ (National Cancer Institute, n.d.). Surgery can remove lung cancer, debulk the tumor if organ preservation is required, or ease cancer symptoms (National Cancer Institute, 2019). Recovery can range from weeks to months, depending on the surgery performed

(American Cancer Society, 2019). The risk associated with lung cancer surgery can be bleeding, blood clots, medication reactions, infections, and pneumonia (American Cancer Society, 2019).

Chemotherapy

Chemotherapy uses drug treatment to stop the growth of cancer cells either by cell death, apoptosis, or preventing division and can be administered orally, via intravenous infusion, injection intrathecally, intraperitoneal, intraarterial, or topically (National Cancer Institute, n.d.). Chemotherapy can shrink cancers before surgical resection or radiotherapy, kill cancer cells after resection or radiotherapy, or work with other therapies to improve treatment success (National Cancer Institute, 2019). The effects of chemotherapy can be related to the type of chemotherapy administered, the drug dosage, cancer type and stage, and a patient's premorbid health status. Side effects of chemotherapy can include killing or slowing the growth of healthy, fast-growing cells causing overall deconditioning, nausea, vomiting, mucosal membranes, and hair loss (American Cancer Society, 2019).

Radiotherapy

Radiation therapy uses high doses of high-energy rays or particles to kill cancer cells or shrink tumors (National Cancer Institute, n.d.). Radiotherapy can be used as the primary treatment alongside chemotherapy when cancer cannot be removed or debulked due to its size or location (American Cancer Society, 2019). Radiotherapy is also used after resection to kill any lingering cancer cells, before surgery to shrink the tumor, treat cancer that has spread distally, or as palliative therapy to relieve symptoms of advanced cancer (American Cancer Society, 2019). Radiotherapy's side effects can include fatigue, nausea, vomiting, anorexia, weight loss, topical dermal changes in treatment areas, and hair loss (American Cancer Society, 2019).

Palliative Care

Palliative care is the treatment or care given to a patient to improve quality of life by preventing or treating cancer symptoms or treatment side effects (National Cancer Institute, n.d.). The goal of palliative care is not curative. However, palliative care can include centesis procedures to remove fluid from the heart and lungs, resection, chemotherapy, or radiotherapy to remove, shrink, or slow cancer-causing pain (National Cancer Institute, n.d.). In advanced NSCLC, palliation therapy can alleviate pain, bleeding, trouble swallowing, breathing difficulties, and obstructed airways caused by invasive tumors (American Cancer Society, 2019). Palliative care can also address the physiological, social, and spiritual problems caused by cancer and treatments (National Cancer Institute, n.d.).

Treatment success can be defined differently depending on the healthcare professional, patient, and caregivers (Islam et al., 2019). Defining treatment success in the early stages is curative and conventionally leads to

cancer remission. However, this may not be possible in advanced cancer stages, where a focus may fall on improving quality of life (Islam et al., 2019). The success of lung cancer treatment depends on multiple factors (Islam et al., 2019).

Chapter 2

2.2 Danish Context

This section will outline lung cancer within the Danish context. The focus will be placed on lung cancer epidemiology in Denmark and identifying the high-risk population. Furthermore, the current lung cancer pathways in Denmark will be explained, the costs for treating lung cancer identified, and the potential costs of a LCSP.

2.2.1 Lung Cancer Epidemiology in Denmark

Epidemiology refers to disease patterns, causes, and control in populations (National Cancer Institute, n.d.). This section will outline the demographics of lung cancer in Denmark, the factors that affect its presence in Denmark, and the measures in place to control the disease.

2.2.1.1 Incidence

Lung cancer incidence is the number of newly diagnosed lung cancer cases in a population over one year (National Cancer Institute, n.d.). The numerator indicates lung cancer cases as a primary diagnosis during a given time, and the denominator represents the population at risk of developing lung cancer (Torre et al., 2015). In Denmark, lung cancer is monitored by the Cancer Registry (CAR) and the Danish Lung Cancer Register (DLCR), which are driven by reports from the National Patient Register (LPR) (Jakobsen et al., 2013). Lung cancer is the second most common cancer in Denmark, with an incidence of 36.8 per 100,000 people in 2020 and up trending (IARC, 2021). Denmark has the sixth-lowest incidence of lung cancer in Europe (OECD, n.d.). Compared to other cancers in Denmark, lung cancer has the second-highest incidence, at 11.8%, and breast cancer at 11.9% (IARC, 2021).

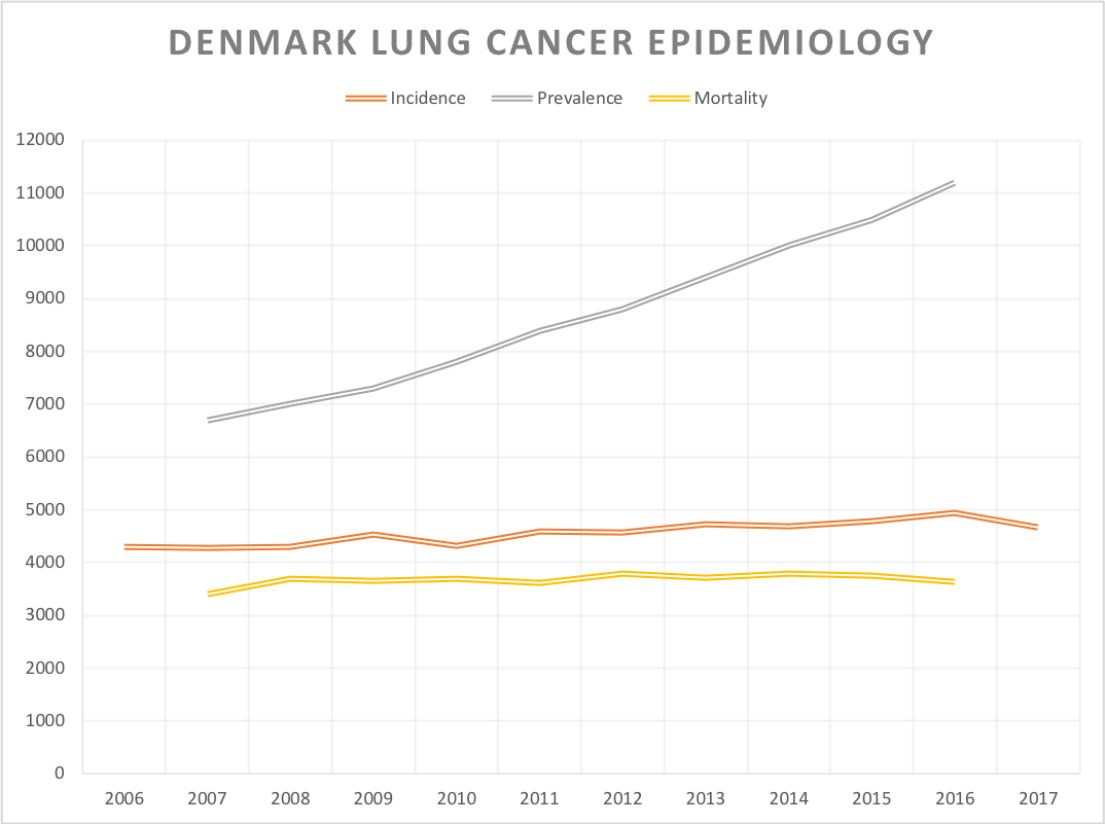
2.2.1.2 Prevalence

Lung cancer prevalence refers to the total number of people in a population who have been diagnosed or have lung cancer and includes people who are receiving treatment, in remission, and are still alive at a specific date (National Cancer Institute, n.d.). Prevalence has increased rapidly in Denmark due to improved survivability post-diagnosis, with a 5-year prevalence of 114.43 per 100,000 (IARC, 2021).

2.2.1.3 Mortality

Lung cancer mortality is the number of deaths in a population from lung cancer over a specific period (National Cancer Institute, n.d.). Lung cancer mortality reflects both incidence and survival, as the numerator includes only deaths, and the denominator is the population at risk of dying from lung cancer (Torre et al., 2015). Lung cancer has the highest mortality rate in Denmark of any cancer, at a stable rate of 27.0 per 100,000 persons in 2020, or approximately 3,700 deaths per annum (IARC, 2021). Denmark has the third-worst mortality rate compared to other EU nations, preceding Poland and Hungary (OECD, n.d.).

Figure 3. Lung Cancer Epidemiology in Denmark



Note. IARC, 2021

2.2.1.4 Survival

Lung cancer survivability is the length of time someone survives following a lung cancer diagnosis (Torre et al., 2015). The survivability depends on the stage lung cancer is diagnosed and the response to treatment (Popper, 2016). The DLCR monitors survivability, and the current lung cancer survivability for Denmark is 1-year 51.4%, 2-year 35.5%, and 5-year 15.9% (Jakobsen et al., 2013).

2.2.1.5 Danish High-Risk Population

The primary etiology of lung cancer development in Denmark is smoking (Guldbrandt et al., 2015). Smoking rates continue to be elevated in Denmark, with 18% of the population smoking daily or occasionally (Danish Health Authority, 2021). The prevalence of smoking has declined since the 1960s, yet smoking rates have stagnated over the past decade (Danish Health Authority, 2021). Other risk factors for lung cancer include COPD and increasing age, which, combined with a high pack-year smoking history, drastically increase the risk of lung cancer development (Jakobsen et al., 2013). When determining the high-risk Danish population, the inclusion criteria for different clinical trials have been used to segment the Danish population, producing varied results. Table 3 below displays the results of the high-risk smoking criteria from the NELSON study and the NLST study.

Table 3. Screening Risk Group in Denmark - NELSON and NLST Risk Group Criteria

Total population ages 55-74 years	NELSON criteria	NSLT criteria
1,325,511	233,756	106,041

Note. Pedersen et al., 2017

Lastly, participant exclusion criteria would limit a person's participation in a LCSP, including recent infections or a history of cancers (Pedersen et al., 2017). As these populations cannot be estimated within this high-risk cohort, the screening cohort may overestimate. Having outlined the main risk factors for developing lung cancer, the next section will present the different methods for identifying and diagnosing lung cancer.

2.2.2 Current Lung Cancer Pathway in Denmark

Like other European nations, Denmark has no LCSP (Guldbrandt et al., 2015). In Denmark, diagnosing lung cancer primarily begins with the general practitioner (GP), with 68.3% of all lung cancer diagnoses involving a GP and the remaining from specialists or acute care settings (Guldbrandt et al., 2015). In 2008, Denmark introduced a lung cancer diagnosis pathway in which GPs could refer a patient to fast-track diagnostics, circumventing traditional respiratory referrals (Guldbrandt et al., 2015). However, many primary healthcare professionals report a lack of awareness surrounding lung cancer among high-risk groups (Moldovanu et al., 2022). Patients are commonly referred for an x-ray over LDCT (Guldbrandt et al., 2015). Guldbrandt et al. (2015) have found that one-third of patients diagnosed with lung cancer had at least two X-rays performed within 90 days of a lung cancer diagnosis, indicating high rates of false-negatives and poor x-ray sensitivity.

Therefore, recommendations have been given for upgraded technologies, such as LDCT, for the fast-track lung cancer diagnostics pathways (Guldbrandt et al., 2015). The nature of lung cancer diagnosis in Denmark means more patients are diagnosed in later disease stages, limiting treatment options and effectiveness (Guldbrandt et al., 2015).

Understanding the extent and seriousness of a cancer diagnosis and determining the best treatment plan begins with staging and categorizing cancer. Staging of lung cancer in Denmark is performed using the TNM system, as previously discussed in section 2.1.1. Treatment in Denmark is aligned with other Western countries, and Denmark has developed and legislated The Cancer Patient Pathways in 2008 for cancer treatment (Probst et al., 2012). Probst et al. (2012) discuss how healthcare professionals developed pathways with the involvement and cooperation of bureaucrats and politicians. The models have allowed for successful national implementation, significantly reducing waiting times and increasing survival. The Cancer Patient Pathways prescribed maximum waiting times for cancer diagnostics and treatment. An example is that surgery and chemotherapy must be offered within 14 and 42 calendar days, respectively, after diagnosis (Probst et al., 2012). As explained by Sørensen et al. (2018), the clinical care offered per lung cancer stage in Denmark was sourced from the Danish national registries from 2005-to 2015 and is listed below.

Table 4. Danish Lung Cancer Clinical Care by Lung Cancer Stage

Danish Lung Cancer Clinical Care by Lung Cancer Stage

Stage	- Resection - Oncology	- Resection + Oncology	+ Resection +/- Oncology	Follow up LDCT
I	6.9%	24.5%	68.6%	3 months for 2 years then 6 months for 5 years
II	8.0%	27.2%	64.9%	4 months for 2 years then 6 months for 5 years
IIIA	9.5%	59.7%	30.9%	5 months for 2 years then 6 months for 5 years
IIIB	14.5%	79.5%	5.9%	6 months for 2 years then 6 months for 5 years
IV	24.1%	73.1%	2.8%	Chest and upper abdomen scan every 3 months

Note. Ekman et al., 2021

2.2.2.1 Cost of Lung Cancer in Denmark

Health expenditure in Denmark accounts for 10.4% of total GDP, providing more comprehensive care than in many other countries in the Organization for Economic Cooperation and Development (OECD) (Tikkanen et al., 2020). Denmark offers universal healthcare paid for by income tax, covering primary and acute healthcare episodes. Estimating the economic burden of lung cancer in Denmark can be done by calculating the annual cost per patient diagnosed with lung cancer and comparing it to the average healthcare costs in the general population (Gouliaev et al., 2021). The study by Gouliaev et al. (2021) calculated the societal and payer perspective costs relating to the treatment of lung cancer compared to the standard population's health care costs. Gouliaev et al. (2021) found the costs of lung cancer in Denmark to be 2.9-fold higher in the decade pre-diagnosis than in the general population and 5.5-fold higher in the decade post-diagnosis.

The costs relating to lung cancer treatment for the years 2013-2015 have been produced by Professor Anders Green in a proposal for a Danish lung cancer screening program (Danish Lung Cancer Group & Saghir, 2021). The costs have been segmented into therapy by no targeted treatment, oncological therapy only, and surgery +/- neoadjuvant oncological therapy. An average treatment cost indicates treatment for late-stage lung cancer to be substantially higher than early stages. Hence introducing ways of detecting lung cancer early should assist in overall cost-containment.

Table 5. Lung Cancer Treatment Costs

Lung Cancer Treatment Costs								
Lung Cancer Stage		- Resection - Oncology		- Resection + Oncology		+ Resection +/- Oncology		Total Average Cost
>=180 days								
I	DKK	134,114.20	DKK	182,636.99	DKK	115,446.27	DKK	144,065.82
II	DKK	79,706.68	DKK	196,911.59	DKK	108,520.77	DKK	128,379.68
IIIA	DKK	124,320.99	DKK	213,505.88	DKK	140,950.86	DKK	159,592.58
IIIB	DKK	113,526.24	DKK	232,169.21	DKK	118,624.10	DKK	154,773.18
IV	DKK	124,455.86	DKK	270,010.64	DKK	171,269.49	DKK	188,578.66
<180 days								
I	DKK	133,009.50	DKK	188,020.28	DKK	110,377.07	DKK	143,802.28
II	DKK	192,454.51	DKK	219,461.84	DKK	81,861.86	DKK	164,592.74
IIIA	DKK	271,076.13	DKK	243,984.14	DKK	141,071.67	DKK	218,710.65
IIIB	DKK	547,639.98	DKK	265,816.61	DKK	130,430.51	DKK	314,629.03
IV	DKK	727,630.57	DKK	401,044.45	DKK	215,262.69	DKK	447,979.23

Note. Danish Lung Cancer Group and Saghir, 2021

2.2.2.2 Cost of a Lung Cancer Screening Program in Denmark

The Danish Lung Cancer Society has submitted a proposal for introducing a lung cancer screening program (Danish Lung Cancer Group & Saghir, 2021). The proposal is currently under review and suggests that additional feasibility trials may need to occur before it can be implemented. Introducing a LCSP will come with budget constraints. The healthcare payer costs for introducing a LCSP have been estimated by Jensen et al. (2020) as € 238/scan based on 2018 prices. They include the costs of participant recruitment, consultations with radiographers and radiologists. Other costs borne by the patient or caregiver are estimated by Gouliaev et al. (2021) and include sick pay, travel costs, and foregone earnings. Costs unable to be estimated but identified by Rasmussen et al. (2015) are the psychosocial consequences of being included in a LCSP and receiving a false positive diagnosis.

3. Literature Review

This literature review will introduce the lung cancer screening trials and cost-effectiveness studies published on LCSPs. According to Pedersen et al. (2017), no study on the cost-effectiveness of a LCSP has been done in the Nordics. This section will first present results from lung cancer screening trials, and then CUA studies that use the RCT outcomes will be outlined and explored for their relevance.

3.1 Lung Cancer Screening Clinical Trials

This section will outline the significant clinical RCTs contributing evidence to support LCSPs. Kaneko et al. (1996) produced the first lung cancer screening trial, which enrolled 1,369 subjects and concluded that using

x-ray alone missed 73% of lung cancers detected by CT scan. Larger and more comprehensive studies have since been produced involving LCSPs which will be outlined in this section.

National Lung Cancer Screening Trial

The Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening (2011), or the National Lung Cancer Screening Trial (NLST), was conducted to determine whether mortality from lung cancer could be reduced with the use of low-dose CT screening versus a chest x-ray. The study is the largest lung cancer screening trial, enrolled 53,454 subjects at high risk of lung cancer from August 2002 - to April 2004 from 33 US medical centers. Participants were aged between 55-74 years, had at least 30 pack-years smoking history, or had quit within the previous 15 years for former smokers. The patients were randomized to undergo 3-annual LDCT or a posterior chest X-ray, with the LDCT arm detecting more cancers than the x-ray control group (1060 vs. 941). Despite a higher incidence of lung cancer, the NLST proved a reduction in mortality in the LDCT group than the control (247 vs. 309), representing a 20% reduction in mortality ("Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening," 2011).

Netherlands Lung Cancer Screening Research

The Dutch-Belgian Randomized Lung Cancer Screening Trial from de Koning et al. (2020), or the NELSON study, investigated screening men primarily and women as a subgroup. It recruited 13,195 men and 2,594 women aged 50-74 years who were current or former smokers with a 15-20 pack-year smoking history. Participants were randomly assigned to undergo LDCT scanning at baseline, year one, year three, and year 5.5, with the control group undergoing no screening. As in the NLST, trial adherence was 90%, with the screening lung cancer incidence of 5.58 per 1000 person-years versus 4.91 cases per 1000 person-years in control. Overall, the NELSON study proved a reduction in mortality of 25% through screening for lung cancer versus no screening (de Koning et al., 2020).

United Kingdom Lung Screening

The UKLS trial from Baldwin et al. (2011) determined whether screening via LDCT and the treatment of early lesions decreased lung cancer mortality compared to a no screening. The study randomized 4,055 people aged 50-75 years with a risk score of developing lung cancer within five years of $\geq 4.5\%$ using the Liverpool Lung Project risk model (LLPv2). The LLPv2 model uses smoking status and duration, respiratory disease history, and family history of lung cancer to determine a person's risk of developing lung cancer. The screening arm detected 86 cancers, with the control detecting 75, with fewer deaths in the screening group than control (30 vs. 46). The relative rate ratio of mortality reduction was 0.65, and a further meta-analysis pooled data from nine trials to determine a rate ratio of 0.86. The UKLS study continued to strengthen the results of the NLST and NELSON study in recommending screening high-risk lung cancer individuals. The study also conducted

a cost-effectiveness analysis to determine the incremental cost-effectiveness ratio (ICER) and QALY performed by Snowsill et al. (2018), which will be discussed further (Baldwin et al., 2011).

Danish Lung Cancer Screening Trial

The DLCST conducted by Wille et al. (2016) compared LDCT versus no screening for lung cancer to conclude if there was an associated reduction in mortality. The study randomized 4,104 participants aged 50-70 years who had a minimum 20-pack year smoking history, with LDCT scans conducted annually for five years. The study identified more early cancers, stage I and II, in the screening group. However, this study did not identify any significant change to lung cancer mortality (Willie et al., 2016).

Additional studies using LDCT as their chosen intervention have been conducted globally, producing positive results in increased detection and reduced lung cancer mortality. The studies investigated LDCT vs. a comparator, risk group categorization, cohort sizes, and outcomes are listed in the appendix

3.2 Cost-Utility Analysis Studies

This section aims to identify and outline CUAs conducted on LDCT screening programs, outlining the costs and benefits gained and the methods applied in the studies. There are currently no CUAs for LCSPs conducted in the Danish context. Most CUAs have been performed in a U.S. context, where the costs differ substantially from Europe (Pedersen et al., 2017; Peters et al., 2022). The CUAs identified and included in this study all have the same comparator, no screening, and the outcome benefits of QALYs and subsequent ICERs. This section will highlight the largest and most comprehensive CUAs performed on LDCT screening programs and provide an overview in the appendix.

Cost-utility Analysis of a Potential Lung Cancer Screening Program for a High-Risk Population in Germany: A Modeling Approach

The paper by Hofer et al. (2018) was created based on the German population aged 55-75 years, comparing an annual and biennial LDCT for 5-years vs. no screening program. Hofer et al. (2018) used the payer perspective with two Markov models to compare the standard clinical care pathway to a LCSP pathway. Costs associated with a LCSP and cancer diagnosis were sourced from the German outpatient reimbursement catalog, and QALYs were taken from the metastudy by Sturza (2010). The starting probabilities were based on the German LUSI study and risk group parameters from the NLST. Transitioning state probabilities were determined using Bayesian calibration methods and German incidence data from the German Center for Cancer Registry Data. The discount rate was set at 3%, reflecting the German statutory health insurer applied rate over a 15-year time horizon. Adherence was set at 54%, with sensitivity and specificity of LDCT and current clinical pathway

derived from current literature. This study produced an ICER of € 30,291/QALY, with a surplus of 0.04 QALYs per person in the screening cohort and a 5-year reduction in all-cause mortality of 2.25%. However, as Germany does not yet have a CET, it was compared to that set by the WHO, and was therefore deemed cost-effective.

Low-Dose Computed Tomography for Lung Cancer Screening in High-Risk Populations: A Systematic Review and Economic Evaluation.

The U.K. metastudy by Snowsill et al. (2018) compared the clinical and cost-effectiveness of LDCT compared to both standard clinical pathways or a single chest x-ray via a Markov model. Adherence was adjusted from 30-47%, with the target cohort aged 60-75 years and 3% risk of developing lung cancer. All-cause mortality rates were sourced from the local statistics, and lung cancer mortality was sourced from the International Association for the Study of Lung Cancer. The cost perspective was the NHS and the Personal Social Services, both government institutions. The primary health outcomes were HRQoL, and life-year attained, expressed as QALYs. A discount rate was applied at 3.5% for costs and QALYs, with the time horizon set as the participants' natural lifetime. The overall findings discovered that the most cost-effective ICER was £28,169/QALY. It was determined not to be cost-effective as it is above the NICE CET guidelines of £20,000/QALY (McCabe et al., 2008).

Cost-Effectiveness and Health Impact of Lung Cancer Screening with Low-Dose Computed Tomography for Never Smokers in Japan and the United States: A Modeling Study

The study by Kowada (2022) compared annual LDCT for lung cancer screening to chest x-ray and no screening via a Markov model. The risk group focused on never-smokers in Japan and the U.S., using a healthcare payer perspective over the lifetime horizon. Detection rates for the U.S. were obtained from the Surveillance, Epidemiology, and End Results Medicare database and the Japanese Cancer Statistic for the Japanese cohort. Transition probabilities were estimated from literature, cancer statistics, vital statistics, and life tables, with detection rates estimated to be equal in both Japan and the U.S. Adherence was set at 100%, with sensitivity and specificity of LDCT and current clinical pathway derived from current literature. A payer perspective was adopted, with costs for screening and cancer treatment taken from Japan based on the Japanese national fee schedule and costs for the U.S. cohort based on Medicare. QALYs were obtained from current literature, with costs and QALYs discounted at 3%. LDCT was found to be more cost-effective for women than men in Japan. However, it was determined to not be cost-effective in the U.S., with an ICER >$100,000/QALY.

There are still inconsistencies seen between CUAs. The methods chosen by each study strongly impact the results, and a country's policies on health economic evaluations can determine if a LCSP will be cost-effective.

Having outlined the methods and results from the most relevant CUAs, this thesis will outline our chosen methods for this EE using evidence supported by the literature.

4. Methodology

The methodology section outlines all of the methodological steps leading up to creating the model for this EE. The first part will outline the inclusion criterias for the model by analyzing existing literature. This will allow the researchers to gain insights leading to decisions for the models' input variables and provide rationale for the choices and assumptions made. Secondly, a framework for the EE will be decided upon in order to answer the research question. The following decisions behind theories, perspectives, and applied frameworks leading up to the model will be explained, and elaborated on. The model's output will be identified as QALYs and costs, with all assumptions within the model addressed and justified.

4.1 Model Scope

This first section will outline the scope criteria for the model, including the screening population, target condition, intervention, comparator, and choice of audience for the EE. This section aims to clarify for the reader which input values the model will be built upon and for whom.

4.1.1 Target Disease

This EE compares different technologies and diagnosis pathways for NSCLC. NSCLC was the chosen disease because it accounts for >85% of all lung cancers and is the most deadly of all cancers in Denmark and globally (Siemens Healthineersn, n.d.). It is also not detected effectively in the earlier stages through the current clinical pathway.

4.1.2 Diagnostic Tool and Comparator

As outlined in section 2.1.2, several different diagnostic tools can be evaluated for the Danish diagnosis pathway of lung cancer. The chosen diagnostic technology evaluated in this thesis is LDCT screening. The motivation behind this choice is that it is the preferred option for a LCSP in today's research (EUnetHTA, 2020). The comparator is Denmark's current lung cancer diagnosis pathway, which is symptomatic presentation. The model is therefore comparing screening through LDCT versus no screening.

4.1.3 Risk Group

The Pedersen et al. (2017) study shows that most studies follow the NLST criteria regarding age and tobacco exposure when identifying their eligible risk group for screening. The screening cohort for this risk group identifies people between 55-74 years old with a ≥30 smoking history or former heavy smokers who have quit within the last 15-years. Based on Pedersen et al.'s. (2017) study, risk groups are filtered using data from the Danish national registries, producing the eligible cohort for the Danish screening program as 106,041 participants (Pedersen et al., 2017). Table 3 in the *Danish High-Risk Population* 2.3.2 shows the identification of the age risk group in Denmark and then the number of people according to the NELSON criteria and NLST criteria.

4.1.4 Choice of Audience

Having the audience and decision-makers in mind will ensure an EE holds relevance to the setting it is applied and reflects the EE's objectives and strengths (Drummond et al., 2015). The primary audience for this thesis is the Danish Ministry of Health, as a LCSP in Denmark would be carried out at a national level and offered free to participants. The Danish Ministry of Health is the primary gatekeeper and decision-maker for universal healthcare in Denmark. The current detection and treatment pathway is provided via primary, acute, and outpatient care (Kristensen & Sigmund, 2008). All costs accounted for in this thesis are the responsibility of the Ministry of Health, as discussed in section 3.1.3, which oversees the general regulation, planning, and supervision of healthcare services and overall cost-control activities (Tikkanen et al., 2020).

The Ministry of Health is a national level organization and is further divided into the governmental authorities; the Health Authority, Medicines Agency, Patient Safety Authority, Health Data Authority, and the Danish Agency for Patient Complaints (Tikkanen et al., 2020). The Danish national authorities have the role of planning mandatory health agreements between the regions and the Local Government of Denmark, negotiating financial reimbursements and agreements on behalf of the regions, and setting performance targets (Tikkanen et al., 2020).

Table 6. Model Scope

Scope of Economic Model	
Target Disease	Non-small cell lung cancer
Diagnostic Tool	Low dose CT
Comparator	Current clinical diagnostic pathway
Risk Group	≥ 30 pack-year smoking history aged 55-74 years
Audience	Danish Ministry of Health

Note. References in text

4.2 Model Foundations

This thesis seeks to evaluate if a lung cancer LDCT screening program for a high-risk population would be cost-effective in Denmark. Therefore, an EE model will be created to calculate the cost-effectiveness between the intervention and comparator previously identified. This section introduces the theoretical foundation which underpins the cost-effectiveness evaluation, perspectives leading the choices of input values, and choices of frameworks.

4.2.1 Viewpoints

This section will introduce the views behind economic analysis, being welfarism and extra-welfarism.

Welfarism

Welfarism is part of welfare economics and is the economic framework for ranking the allocation of resources (Hurley, 2014). All economic systems face problems associated with resource allocation and the distribution of resources efficiently and equitably. Welfare economics is built upon four central tenets; (1) utility maximization, (2) individual sovereignty, (3) consequentialism, and (4) welfarism (Hurley, 2014). Utility maximization refers to the assumption that behavior will dictate rational choices and preferences. Individual sovereignty is the term that individuals themselves best judge one's welfare. It notes that individual evaluations and preferences are respected. Consequentialism refers to any policy or resource allocation being judged on the effects that flow from the policy . Welfarism refers to the benefits of any policy being judged by the attained utilities of the included cohort. Modern welfare economics also include the Pareto criterion, where resources

cannot be reallocated to increase one cohort's utility without decreasing another. The welfarist approach can be made through a cost-benefit analysis (CBA). Employing the use of a welfare-economic framework can present challenges. The Pareto criterion can lead to policy paralysis if resources need to be reallocated from one group to another in society. Also, the only outcome which can be measured is utilities. With efficiency defined as the Pareto criterion, the policy is only deemed efficient if there is a positive net benefit (Hurley, 2014).

Extra-Welfarism

Extra-welfarism is the economic framework evaluating a policy based on larger volumes of information and additional inclusions (Hurley, 2014). The economic approach was developed to compensate for the priority setting required in healthcare and offers differing outcomes rather than simply the preferences and utilities gained by society. Extra-welfarism places health at the center of health policies and considers other factors beyond the welfarist approach. Brouwer et al. (2008: p.14-15) states four ways in which welfarism and extra-welfarism differ from one another:

1. *It permits the use of outcomes other than utility*.
2. *It permits the use of sources of valuation other than affected individuals*.
3. *It permits weighing the outcomes (whether utility or other) according to principles that need not be preference-based.*
4. *It permits interpersonal comparisons of well-being in various dimensions, thus enabling moving beyond Paretian economics.*

   (Brouwer et al., 2008: p.14-15)

The difference arose from multiple objections within the welfarism framework. Firstly, assigning a monetary value to lives saved can be deemed unpalatable, which has given rise to CUAs over CBAs in evaluating health care policies and interventions (Hurley, 2014). Secondly, as healthcare consumption and resource allocation is performed out of need, the WTP threshold should be circumvented, and access to healthcare ideally be independent of the ability to pay. Thirdly, a "decision-maker" approach has formed, whereby the analyst assists in achieving the stated goals of the decision-makers. Fourth, the demand for health and healthcare has presented consumption efficiency and supply issues. An extra-welfarist approach allows for assessing the effectiveness of a health care service by measuring the health effects after its consumption (Brouwer et al., 2008).

An EE undertaken through an extra-welfarist framework would use the Cost-effectiveness analysis (CEA) or CUA methods (Hurley, 2014), where health benefits can be optimized under restricted budgets. Providing outcomes using this approach can assist decision-makers in making informed choices, as it can accommodate

for distributional and procedural equity, ensuring fairness in resource allocation (Hurley, 2014). This thesis uses an extra-welfarist approach to focus on the CUA methodology as it is adaptable and can include individual utility and other relevant outcomes (Brouwer et al., 2008). The CUA framework and alternative frameworks are explained more in detail in the following section.

4.2.2 Economic Evaluation Frameworks

This thesis aims to conduct an EE to guide the Danish Health Authorities in making decisions that give the most benefit at the lowest cost (Drummond et al., 2015). The framework for EE is used in order to compare different alternatives to analyze the cost and health outcomes (Drummond et al., 2015). As explained below, Drummond et al. (2015) list four main reasons why EEs are important:“

1. *Without systematic analysis, it is difficult to identify clearly the relevant alternatives*
2. *The perspective (or viewpoint) assumed in an analysis is important*
3. *Without some attempt at quantification, informal assessment of orders of magnitude can be misleading*
4. *Systematic approaches increase the explicitness and accountability in decision-making*

   (Drummond et al. 2015, p. 2-3).

The two main features of EE include dealing with both the inputs, described as *costs*, and outputs, described as *consequences*, and providing several choices because resources are limited (Drummond et al., 2015). These two attributes aid in decision-making as all desired outputs cannot be produced. These two characteristics lead to EE's definition: "*the comparative analysis of alternative courses of action in terms of both their costs and consequences"* (Drummond et al. 2015, p. 4). This definition creates the formula for arriving at the cost-effectiveness stage, where the cost and effects of one alternative are compared to the cost and effects of the second alternative.

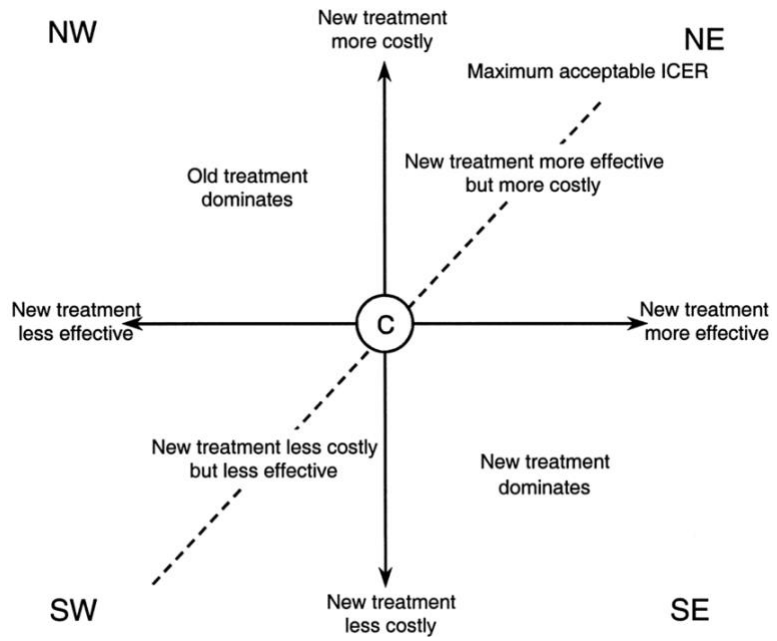
$$\frac{Cost\ intervention\ A - Cost\ intervention\ B}{Effect\ intervention\ A - Effect\ intervention\ B} = Incremental\ Cost - Effectiveness\ Ratio\ (ICER)$$

The output of the EE is usually expressed as an incremental cost-effectiveness ratio (ICER), the ratio of the incremental costs and effects between the alternative interventions (Drummond et al., 2015). An ICER can capture the output of the Markov model and systematically present this information. The ICER has been used routinely within HTA to summarize the results of EEs (Paulden, 2020). For this thesis, the decision-maker is provided with an estimate of how much one more unit of effect will cost if Denmark implements the potential LDCT screening program.

The ICER is usually illustrated in a cost-effectiveness plane (CEP), falling in the northeast, southeast, southwest, or northwest quadrant of the cost-effectiveness plane (Briggs & Tambour, 2001). The intervention

is always cost-effective to its comparator if the ICER falls in the southeast quadrant, with higher effects at a lower cost. The intervention is not cost-effective if the ICER falls in the northwest quadrant, leading to a lower effect at a higher cost. For the northeast and southwest quadrants, the ICER has to be put in relation to a defined cost-effectiveness threshold (CET) to determine the cost-effectiveness. If the ICER falls below the CET, it is considered cost-effective, since the intervention will either cost less with a more negligible effect or cost more with a higher effect, as displayed in figure 4. Displaying the ICER results, falling on, above, or below the CET, will assist the decision-maker in determining if an intervention is cost-effective (Briggs & Tambour, 2001). The concept of the CET will be further explained in section 3.2.2.

Figure 4. Cost-effectiveness Plane



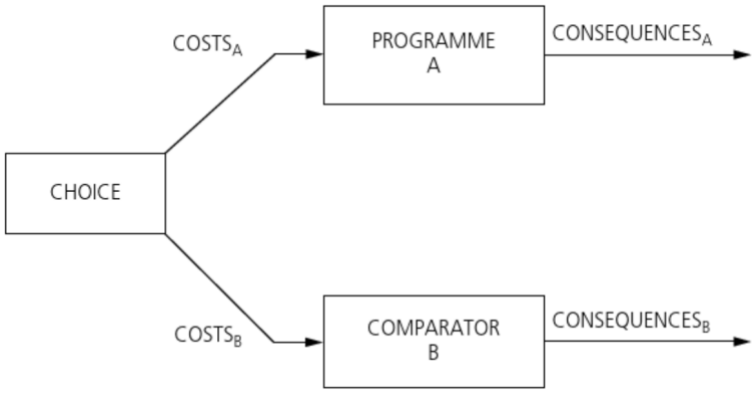
Note. Briggs & Tambour, 2001

There are limitations to using ICERs as a measure of cost-effectiveness. First of all, a CET is required to determine the cost-effectiveness. Secondly, a reduction in the ICER does not necessarily imply that an ICER has become more cost-effective (Paulden, 2020). Variation in the assumptions can lead to changes in the comparator and the intervention group; hence using the ICER as a guide can be misleading. This thesis has sought to overcome this by investigating the granular details within the model's output to explain changes, such as the epidemiological benefits gained. However, in doing so, measuring the net benefits without a threshold or context can lead to results that lack meaning. Other studies have identified limitations to ICERs when evaluating screening interventions that suggest the *Relative net benefit* as an alternative method (O'Mahony, 2015). The research shows that improvement in screening could enhance cost-effectiveness. However, this improvement might not be reflected in the ICER "because the whole efficient frontier may shift

when all strategies are affected by a common technological change, so ICERs on the frontier can be insensitive to this improvement" (O'Mahony, 2015, p. 705).

To summarize, the task of this thesis includes identification, measuring, valuing, and comparing costs and consequences between choices being (1) the introduction of a LCSP through a LDCT and (2) no LCSP or the current diagnosis pathway for lung cancer in Denmark. The relation between the two features is illustrated in Figure 5 below.

Figure 5. Illustration of the Two Features of an Economic Evaluation



Note. Drummond et al. 2015, page 4.

There are several different EE frameworks used in healthcare, the foremost being; CBAs, CEAs, and CUAs (Shiell et al., 2002; Rudmik & Drummond, 2013). These originate from different views and underlying theoretical frameworks, identifying and measuring different effects or consequences. Each framework is preferred by different stakeholders and comes with advantages and disadvantages (Drummond & McGuire, 2001). This thesis will follow the CUA stemming from an extra-welfarism viewpoint. The following paragraphs will outline the different EE frameworks and the motivation behind conducting a CUA.

4.2.2.1 Cost-Utility Analysis

In this thesis, the chosen EE method is the CUA, the most widely published form of EE (Drummond et al., 2015). The CUA is similar to the CEA and originates from an extra-welfarist viewpoint, calculating the ICER using costs and effects. However, it uses a generic measure of health gains (not natural units) which allows for comparisons between interventions and programs in different areas within health care, requiring only one CET (Drummond et al., 2015). The generic outcome measure is usually expressed as either quality-adjusted life years (QALYs) (Drummond et al., 2015) or disability-adjusted life- years (DALYs) (Tan-Torres Edejer et al., 2003).

QALYs are the most common measure of health effects and measure effects in terms of quality and quantity of life years (Weinstein et al., 2009). The QALY is a preference-based measure on a scale that reflects the level of health status from zero to one, with zero being equal to *death* and one being equal to *perfect health*, further explained in section 3.3.2.2. The incremental cost and effect of the evaluated intervention are then expressed in *cost* per *QALY*, or the ICER (Drummond et al., 2015). The ICER will be the end output of this thesis, and together with the CET, this output can help guide the decision-makers (Drummond et al., 2015).

Like other EE methods, the CUA can be criticized in several ways. The limitations of conducting a CUA are that it assumes risk-neutrality and does not account for uncertainty in outcomes (Drummond et al., 2015). An example of this is that people would value five additional life-years of full health the same as having 50% reduced health at ten years or a 50% chance of instant death because of, e.g., side effects of lung cancer treatment. CUAs require a CET, further explained in Section 3.2.2. An additional criticism is that QALYs are the same for each individual. Firstly, patients' preferences for health might differ. For example, a youth athlete may value health more than someone elderly (Drummond et al., 2015). Secondly, 0.2 QALYs are the same for people near death as for people in near-perfect health. Thirdly, CUAs remove individual utility as they violate equality, societal preference and fairness (Senera, 2021). The CUA also includes the limitations of QALYs (or DALYs), further explained in section *Benefits.*

4.2.2.2 Cost-Effectiveness Analysis

The CEA compares alternative interventions' costs and benefits similar to the CBA. However, the health benefits are measured in natural units and not in monetary terms (Drummond et al., 2015). Natural units can be life years *gained, disability years saved,* or *point of blood pressure reduction.* This method believes that it is too narrow using only individual preferences, such as utilities used in CUAs for EEs, since health is a merit good (Drummond et al., 2015). Therefore, this extra-welfarism framework includes more perspectives than the individual utilities, including decision-makers, population samples, and clinical experts (Brouwer et al., 2008). The CEA can reflect a societal benefit of health and not simply focus on the individual's WTP. The CEA is mainly used when the decision-maker has a given budget and considers a limited range of options within a given field (Drummond et al., 2015). The cost-effective alternative is the one with the highest benefits and lowest cost.

The limitations of this evaluation method are that, firstly, the benefits are difficult to communicate to decision-makers since it is expressed in natural units. Studies on diagnostics or prevention interventions usually focus on the specific impact of the intervention and not the patient's broader health (Drummond et al., 2015). The method requires specific CET for all different disease areas, a process that is impractical and politically infeasible. Therefore, using this type of EE for this thesis would not be feasible since there is no assigned CET

for lung cancer (Cameron et al., 2018). Lastly, the specific measure used, or natural units, makes it difficult to assess the opportunity cost (i.e., benefits forgone) in other interventions covered by the same budget (Drummond et al., 2015). In turn, a generic measure must be used in a CUA, as explained above.

4.2.2.3 Cost-Benefit Analysis

The CBA measures health outcomes in monetary terms, and the result can be stated as a sum or a ratio of cost to benefits (Drummond et al., 2015). The value of expressing the benefits and costs in monetary terms enables comparisons with two or more treatment alternatives or even non-health-related programs. The results can also be easily communicated to decision-makers transparently (Gov.UK, 2020). This method follows a welfarism framework that puts the individual in the center. It believes that individuals are rational and capable of choosing options, in this case, healthcare interventions, that give them the highest welfare (Hurley, 2014).

The CBA tries to mimic the private market without distortion by measuring the population's willingness to pay (WTP). This monetary valuation of benefits for different interventions is usually obtained through (1) stated preferences/contingent valuation, such as WTP surveys or discrete choice experiments, or through (2) revealed preference, such as the human capital approach or wage risk studies (Drummond et al., 2015). The individual focus and data collection create critiques of the framework (UK Health Security Agency, 2020).

There are several critiques to this method, justifying its disuse for this EE. Firstly, it assumes rationality that in order to calculate the ICER, the health benefits are turned into monetary value. The question is then proposed, are individuals able to express monetary values to health outcomes? It assumes no externalities or spillover effects, such as overlap between individual utility functions. It accepts the current income distribution that individuals from different SES with the same intervention benefit will assign different WTP for the intervention (Drummond et al., 2015). Furthermore, this thesis evaluates two interventions from an extra-welfarist approach, which do not have to be compared to a non-health-related program. Due to these critiques, the CBA evaluation method was not chosen for this thesis.

Table 7. Summarizing the Different Economic Evaluation Frameworks

EE	Measurement of cost	Measurement of effects	Suitable for
CBA	Monetary units	Monetary units	When non-health effects are also important, activities across society are being compared (Sundhedsstyrelsen, 2008)
CEA	Monetary units	Natural units	When activities with the same measure and purpose of effectiveness are compared (Sundhedsstyrelsen, 2008)
CUA	Monetary units	Generic measure of healthy years, normally measured as QALYs	When comparing interventions across the health care sector (Sundhedsstyrelsen, 2008)

Note. Drummond et al., 2015, page 4; Kristensen & Sigmund, 2008; Sundhetsstyrelsen, 2008

Table 7 summarizes the main EEs for comparison of healthcare interventions. To conclude, choosing a CUA for this study is because CUAs are the most favorable type of EE (Drummond et al., 2015). The CUA makes it possible for the decision-makers to compare the cost-effectiveness results of the two alternatives to other diseases and treatments using the generic QALY measurements. CUAs originate from an extra-welfarism viewpoint, including more than just the individual preferences, which provides importance, considering that health is a merit good. However, the CUA requires a CET for the cost-effectiveness analysis. Therefore the next section will explain the concept behind the threshold and the threshold used for this thesis.

4.2.3 Cost-Effectiveness Threshold

The CET is important for CUAs to determine if an intervention is cost-effective (Drummond et al., 2015). The CET is the maximum amount that a decision-maker would pay for a unit of health outcome (York Health Economics Consortium, 2016). The calculated ICER in this thesis should, in other words, be below a certain threshold for the intervention to be cost-effective. The CET is not being calculated as a part of the CUA but is previously established and guides the interpretation of the cost-effectiveness output decision (York Health Economics Consortium, 2016). Even though EEs are a mandatory part of the HTA process in several countries, an explicit CET value has never been established to assess new health care technologies (Santos et al., 2018). This section will explain the different methodological approaches for defining the CET, outline the most common measure for CETs, and provide a table with implicit and explicit CETs identified by different

European countries, the US, and Canada. It will then present the Swedish CET as the chosen CET for this thesis.

Research on CETs usually suggests a definition through three main approaches: (1) the willingness-to-pay (WTP) method, (2) the precedent method, and (3) the opportunity cost method (Santos et al., 2018). The WTP method represents the welfare economics theory, previously explained in section 3.3.1. The CET is estimated through preference data collected from the population using the WTP method (Santos et al., 2018). The values are collected through either contingent valuation surveys or indirectly from people's behavior in the market. Santos et al. (2015) state that "these methods are intended to elicit the maximum value that an individual would be willing to disburse to obtain a determined amount of health improvement, usually a small difference in utility aggregated to generate the value for a quality-adjusted life-year (QALY)" (p.278). This method can be questioned for the same reason that the CBA and welfarism viewpoint can be criticized. Putting individual preferences in the center leads to detachment from the budget-setting process (Santos et al., 2018). This thesis will not use this method since this kind of CET data is unavailable in Denmark. Furthermore, this thesis follows an extra-welfarism viewpoint conducting a CUA, making the WTP method inappropriate.

The second method for determining the CET is the precedent method, which identifies cost-effectiveness among approved and funded technologies (Santos et al., 2018). Society already pays for technologies and alternatives with higher efficiency, which should be approved. This threshold depends on evaluating existing technologies and assumes that previous decisions have been taken rationally. This method is questioned because it runs the risk of uncontrolled growth in healthcare expenditures, does not consider the affordability of interventions, and could lead to fewer gains and more losses in health outcomes (Santos et al., 2018). This method is not used since there are no available screening programs for lung cancer today.

The third approach is the opportunity cost method, which "It assumes that the budget will be fully spent trying to obtain the maximum possible health returns by allocating from the most efficient to the least efficient interventions" (Santos et al., 2018, p. 279). The measure for opportunity cost is expressed in forgone health benefits, including QALYs or DALYs. This CET cannot be calculated independently of the healthcare budget nor for new technologies that would impose further costs on the healthcare system and maybe provoke displacement of the already funded interventions (McCabe et al., 2008; Culyer, 2016; Vallejo-Torres et al., 2016). It suggests that multiple thresholds may be required because different interventions are associated with different costs and opportunity costs (Santos et al., 2018). It suggests separate budgets for different interventions in the same healthcare system, meaning that optimal reallocation involves the expansion of cost-effective interventions and displacing those less cost-effective (Santos et al., 2018). Although, the discussion about how to best estimate the threshold through the opportunity cost measure is divided. Some suggest that estimating the CET through a *league table* (Vallejo-Torres et al., 2016) or a *bookshelf model* is better.

Santos et al. (2018) explain that "A cost-effectiveness league table lists alternative therapeutic strategies in order of desirability based on their ICERs and allocates them until the limit of the budget is reached" (p.279). The *bookshelf model* represents the league tables differently and consists of bi-dimensional graph computing. This figure provides the health benefit that the society would get if they used the specific intervention explored. Although these methods are adequate since they combine measures of affordability and efficiency, as well as outline the cost and benefits of all alternative health interventions, they are challenging to construct because of data availability. Another limitation is that these methods do not consider the potential lack of information about the alternatives. Furthermore, it does not consider other objectives of the healthcare system, such as social inequalities or access to innovation (Santos et al., 2018). Some less effective technologies might be necessary for certain groups of patients who will not get the treatment because other interventions are more suitable for other groups and are more cost-effective. This thesis cannot apply this approach either because of poor data availability on cost and benefits.

The different approaches to arriving at a CET come with benefits and limitations. Many countries do not have an established threshold due to the controversy regarding the use and the methods for arriving at an appropriate threshold value (Vallejo-Torres et al., 2016). Some also argue that setting an explicit threshold could incentivize manufacturers to raise their prices to the ICER level (Soares Santos et al., 2018). Adopting high threshold levels could increase health expenditures and decrease health coverage (Newall et al., 2014; Culyer, 2016; Revil et al., 2014). However, establishing an appropriate method for the threshold could also improve the value for money in healthcare and bring transparency to the decision-makers (Soares Santos et al., 2018). Internationally the most referred CET is based on years of perfect health and is referenced by the Commission on Macroeconomics and Health published by the WHO (Newall et al., 2014; Bertram et al., 2016; Marseille et al., 2015; WHO, 2001).

The objective of the international threshold is to be able to associate the national benchmark with affordability (Eichler et al., 2014). This threshold should reflect more factors than market income, such as pain, suffering, and life longevity, and it tries to because the value is a utility-adjusted life year (Newall et al., 2014). The WHO's (2003) approach defines the threshold being one to three times (3x) gross domestic product (GDP) per capita (Griffiths et al., 2015) per DALY. In Denmark the GDP per capita was 395,300 DKK in 2020 (Statista, 2022) resulting in a CET between 395,300 to 1,185,900 DKK (395,300*3=1,185,900). Although this threshold has been used in EEs around the world, WHO is trying to dissociate themselves from this recommendation in later years because it is unfit for many contexts (Marseille et al., 2015; Bertram et al., 2016; WHO, 2016; WHO, 2001) and criticized by many health economists (Newall et al., 2014; Revil et al., 2014). This method is usually higher than the opportunity cost threshold (Bertram et al., 2016; Claxton et al., 2015; Woods et al., 2016; Marseille et al., 2015) and could offer a poor constraint when trying to incorporate new interventions into the health system. This method does not discriminate between interventions effectively and does not

compare what is considered good or bad value for money. Therefore, using this method could lead to unrestrained budget increases without foreknowledge if these lead to health gains or losses (Santos et al., 2018).

Most countries have not established an explicit CET; however, some have an implicit threshold (Vallejo-Torres et al., 2016). The UK's National Institute for Health and Care Excellence (NICE) reports a maximum threshold value that the healthcare system uses as a WTP for a QALY. This threshold ranges between £20,000 to £30,000 per QALY (NICE, 2015). Other countries recommend specific ranges or figures, but these have not been formally adopted (Vallejo-Torres et al., 2016). Table 8 below summarizes the recommended CETs in some European countries, the US, and Canada.

Table 8. Implicit or Explicit Thresholds in European Countries, the U.S., and Canada

Country	Threshold (Local Currency)	Threshold (DKK)	1*GDP per capita (DKK)	3*GDP per capita (DKK)
England	20,000 - 30,000 GBP/QALY mostly used 50,000 GBP/QALY for extending life treatments in end-of-life care	179,148 - 268,721 DKK/QALY mostly used 447,869 DKK/QALY for extending life treatments in end-of-life care	279,990	839,970
Ireland	45,000 EUR/QALY	334,730.32 DKK/QALY	581,460	1,744,381
Poland	146,241.8 PLN/QALY	234,245.62 USD/QALY	107,205	321,614
Sweden	Between 700,000 and 1,220,000 SEK/QALY	Between 505,672 and 881,315 DKK/QALY	356,467	1,069,402
The United States	Not defined, but there is a resilience of the value of 50,000 to 100,000 USD/QALY cited in USA-based CEA	Not defined, but there is a resilience of the value of 340,960 - 681,921 DKK/QALY cited in USA-based CEA	433,654	1,300,962
Canada	50,000 CAD/QALY	271,808.29 DKK/QALY	295,238	885,713

Note. Soares Santos et al., 2018

* All currencies were converted 2022-04-14 to DKK with the Official Exchange Rate from the Global Exchange.

* All GDP per capita are from 2020 derived from the World Bank Data (2022).

NICE in the UK has operated with an explicit value since 2004. The threshold of 20,000 GBP/QALY is set, but it can be higher considering: "certainty of ICER; inadequately evaluated health-related quality of life; innovation; and other non-health objectives of NICE" (Santos et al., 2018, p.6). The 50,000 GBP/QALY can be used if the technology prolongs life in terminal care (Paulden et al., 2014; Claxton et al., 2015; Schwarzer et al., 2015; Bertram et al., 2016).

Ireland legally established a threshold of 45,000 EUR/QALY in 2012. New pharmaceuticals with an ICER below this threshold will have a guaranteed reimbursement (Santos et al., 2018). Poland's general threshold follows the international WHO threshold of three-fold GDP per capita/QALY (Grzywacz et al., 2014; Jakubiak-Lasocka et al., 2014; Bertram et al., 2016; Matusewicz et al., 2015). Sweden uses an implicit threshold between 700,000 - 1,220,000 SEK/QALY (Santos et al., 2018). Although the rule-of-thumb threshold in Sweden is 500,000 SEK, approval is between 91% for non-severe and 98% for severe diseases (Svensson et al., 2015). Many publications in The United States refer to a threshold value between 100,000 - 150,000 USD/QALY. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not have an explicit CET, but 50,000 CAD/QALY is often cited. The Netherlands and Norway are not included in the table because they do not have a formal CET. Although, the Health Care Insurance Board, Zorginstituut Nederland, suggests a range between 10,000 - 80,000 EUR/QALY (Franken et al., 2014), and in Norway, it is common to see a threshold of 500,000 NOK/QALY cited in the literature (Burger et al., 2014; Samdal et al., 2009).

To decide on a threshold for this thesis' analysis, one must consider all the different approach options previously mentioned. The first three main approaches are not chosen due to lacking data availability about the cost and benefits of screening programs in Denmark. The analysis will instead choose the Swedish implicit CET for the primary analysis. Sweden is similar to Denmark, a high-income country with the same Beveridge health care system model. Sweden and Denmark are also neighboring countries sharing similar cultures and health standards.

Regarding the threshold ranges, it can be assumed that cancer programs would probably be in the upper CET range since cancer historically has been given a large budget proportion compared to other diseases worldwide (Field et al., 2016). Therefore, the primary threshold used in this thesis will be 881,316 DKK/QALY, and a second analysis will use the international threshold of 1,185,900 DKK/QALY. The reason for why the international threshold is applied to QALYs instead of DALYs is because of Poland's interpretation of the international threshold, being applicable to QALY values too. Having decided on the CET, the next step will be to identify the cost and QALY data used in the economic model. After deciding upon the model scope and

foundation, a decision model has to be developed to organize the cost and benefit data correctly and aligned to the different diagnosis pathways. The model development is further explained in the following section.

4.3 Decision Analysis and Model Development

The following steps is to decide on the method for gathering and handling the cost and benefit data. There are two main ways of doing this: firstly, through a *trial-based EE*, where data comes from one single source, usually a RCT. This method collects data from a sample of study participants or patients (Drummond et al., 2015). Research indicates that this method comes with many limitations and EEs for decision-making usually need to use evidence from different sources (Drummond et al., 2015). Decision-analytic modeling has a growing use as the second vehicle for EEs. This method combines evidence and data from several different sources such as RCTs, observational studies, surveys, resource use, outcome data, etc. According to Drummond et al. (2015), the decision model brings together meaningful evidence to answer a specific healthcare decision problem at a point in time and specific jurisdiction. The decision-analytic modeling method is preferred over the trial-based EE because of the inclusion of multi-source research data. This thesis will follow the decision-analytic modeling approach, further explained in the following sections.

4.3.1 Decision Analytic Modeling

The decision-analytic modeling is used for clinical decision-making regarding patients under conditions of uncertainty (Drummond et al., 2015) and when the cost does not have to be the primary consideration (Hunink et al., 2014; Weinstein & Fineberg, 1980). Drummond et al. (2015) further state that a decision-analytic model "defines a set of mathematical relationships between entities (usually health states or pathways) characterizing the range of possible disease prognoses and the impacts of alternative interventions" (p.312). This information benefits EE because the entities predict costs and health effects quantities. This method further satisfies five other central objectives in EE, being the following:

> *Structure* - Provides structure on prognoses of patients in question and how interventions affect these prognoses. The patients may be healthy or asymptomatic but will often have a particular condition that is being explored.
>
> *Evidence* - The structure of the model and the estimates of input parameters offer an analytical framework with a full range of evidence.
>
> *Evaluation* - It makes it possible to compare two options, going from relevant evidence to estimates of cost and effects.

Uncertainty, variability, and heterogeneity - The model assesses uncertainty in the structure and input parameters related to the evaluation.

Future research - By assessing uncertainty, it can identify priorities for valuable future research.

Drummond et al. 2015 p.312

Decision-analytic models also serve two essential activities for EEs; measurement and decision analysis (Drummond et al., 2015). The first relates to measuring data related to effectiveness, unit costs, resource use, and health-related quality of life (HRQoL) weights. The decision analysis is about synthesizing the relevant evidence in decision uncertainty. This thesis is conducting decision-analytic modeling as it uses several sources and RCTs in the data collection. The following sections will explain the requirements for conducting an EE through this approach.

Drummond et al. (2015) outline six requirements for EEs being:

"They need to compare all options;

The need to reflect all relevant evidence;

The need to link intermediate to final endpoints;

The need to extrapolate over the appropriate time horizon of the evaluation;

The need to make results applicable to the decision-making context;

Using models to assess heterogeneity."

(p. 314-322).

The first stresses the importance of assessing all relevant options to evaluate the value for money. This thesis presents the different screening options, and in section 3.2.1, the motivation is outlined behind the choice of evaluating the LDCT scan versus the current clinical pathway. The researchers assess previous EEs and RCTs on LCSPs, concluding that LDCT screening is the preferred intervention for screening for lung cancer. This thesis is also transparent in outlining all the different screening options in the background information so that the reader or decision-maker is informed of the different available options.

The second requirement is bringing all relevant evidence to the decision-maker (Drummond et al., 2015). Evidence in EEs must display effectiveness and resource use, HRQoL, unit costs, and parameters and how these will change over time. This thesis collects data from a range of sources compared against each other. The

results from RCTs for LCSPs are explained in the literature review and the previous CUAs within the field. The costs and QALYs are explained in detail in the *Perspectives* section and the parameters are explained further in the following sections. The researchers have identified the main RCTs on LCSPs and the most comprehensive CUAs on LCSPs worldwide. Based on this evidence and cost data from the Danish context, relevant evidence was used for this study.

The third requirement is fulfilled when the EE makes meaningful measurements of effects related to the ultimate health measures (Drummond et al., 2015). This study avoids the intermediate endpoints and links intermediate to final endpoints by investigating the diagnosis linked to a final health outcome. It will link the transitions between health states, diagnosis stage, or death states, and then the diagnosed patients will be followed to the death stage. This EE will look at changes in mortality when introducing a LCSP compared to the current clinical pathway in Denmark. The utility measure will be further presented in the benefits section 3.3.2.2.

The fourth requirement regarding time evaluation is essential for decision models. These bridge the gap between observed data from trials and forecasting what is expected to happen with costs and effects over a longer time horizon (Drummond et al., 2015). By comparing the available data options, one has to extrapolate and make appropriate assumptions about the future development of QALYs, death, and cost data. The choices will significantly affect the EE outcome when extrapolating data and making assumptions. The probabilities of moving to different stages in the model will be further explained in section 3.2.2.1. A Markov model will be created using the data to estimate the future costs and QALYs over a more extended period.

The fifth requirement also holds that the model relates and combines other available evidence to make the results applicable to a decision-making context that answers our research question. Many RCTs only explore specific areas and do not cover the complete scope needed in a decision-making context. However, the decision model combines evidence to make this possible.

The sixth and last requirement is assessing heterogeneity between subgroups in the broader population. The intervention evaluated might be cost-effective for some patient groups but not others (Drummond et al., 2015). If one fails to reflect heterogeneity in EEs, this can lead to costs for the healthcare systems and lost opportunities for health gains, and wasted resources. This thesis focuses on one specific subgroup of lung cancer; participants aged 55-74 years with a 30-pack-year smoking history.

Key Elements and Stages of Decision-Analytic Modeling

Once all the six requirements for EE are fulfilled, the critical elements of the decision analysis have to be identified. These include (1) *probabilities*, reflecting changes in health or likelihood of events such as death and disease progression, and (2) the *expected values* of cost and effects, where each alternative intervention follows possible pathways resulting in different outcomes (Drummond et al., 2015). There are also four main stages to follow when developing decision-analytic models. (1) Define a decision problem by identifying the question to be answered, interventions being compared, and the recipient group. (2) Defining the model boundaries and what the model should include and exclude. (3) Conceptualizing the model, structure the model. (4) Implement the assumptions and impacts of interventions in a specific model (Drummond et al., 2015). The quality and validity of the model are determined by the quality of evidence used and the structural assumptions the model is built upon. This thesis will create two models, (1) a *decision tree* and (2) a *Markov model*, to answer the thesis' research questions. The models' choices of evidence and structure are further explained below to uphold the highest quality and validity.

4.3.1.1 Decision Tree

Drummond et al. (2015) explain that the decision tree "represents individuals' possible prognoses, following some sort of intervention, by series of pathways" (p.328). The decision tree consists of *decision nodes*. This model starts with outlining the decision to either implement a LDCT screening program or keep the current lung cancer detection pathway, visualized in Figure 7 as the square box to the left. It also consists of *chance nodes*, which characterize the range of different events that can happen to patients, visualized in circles (Drummond et al., 2015). Each chance node is then related to *branch probabilities*, the chance that different events may happen to the patient in that part of the tree. Moving from the left to the right in the model illustrates subsequent possible events with *conditional probabilities* since the previous events will determine the next step's probability. The combination of such linked events is called *pathways* and illustrates the different events a patient can experience through the tree. Each pathway consists of events, probabilities, and is mutually exclusive, meaning that one individual can only follow one pathway (Drummond et al., 2015). Normally the purpose of the decision tree is to illustrate and calculate the cost and effects for each pathway by using the probabilities associated with each chance node. The expected cost and effects for the total number of people are then calculated by weighting each pathway's cost with the probability of that pathway and summing all the possible pathways (Drummond et al., 2015).

A limitation to decision trees is that they quickly get complex with multiple branches. Over time a patient can face new events, making the decision tree even more complicated and "bushy" (Drummond et al., 2015). Usually, one illustrates the decision tree as a simplified version of reality to avoid the messy and complex

illustration. Another limitation of using a decision tree for developing a decision model is that the decision tree does not define time, time-dependent elements are challenging to consider and implement. Furthermore, adjusting for mortality over time when calculating the QALYs is complicated (Drummond et al., 2015). The following steps follow Drummond et al. 's (2015) four stages to developing the decision tree model, built on the previously described theory.

Stage 1: Decision Problem

This model is constructed to illustrate the patient pathways for the LDCT screening cohort versus the current pathway. The main goal for this decision tree is purely illustrative and its purpose is not to help in calculating costs or QALYs. This is due to the nature of the screening intervention, making it more feasible to calculate costs and benefits using a Markov model explained in the following chapter. Decision trees cannot define time, and the cost and QALY data will be the same in the output of one "cycle" in the decision tree. The output would, therefore, not be relevant to compare.

Stage 2: Model Boundaries

The model boundaries for the decision tree follow the model scope in terms of explored disease, intervention options compared, and cohorts or risk groups. False positive rates and post-diagnosis progression are not included.

Stage 3: Conceptualizing the Decision Model

The critical stage when developing a decision model is to decide on the structure and how to relate the input parameters to each other (Drummond et al., 2015). How should the probabilities, costs, and QALYs be interconnected with each other to result in an output that helps decision-makers? This thesis identifies the different pathways that patients can potentially take in the diagnosis process of lung cancer in Denmark. It compares a screening group to a non-screening group to illustrate the different possible decision branches. The cohort in both the LDCT screening and non-screening group are 106,041 people.

The first chance node consists of all cause mortality and all individuals must pass through this pathway. The chance of dying of all-cause non-related lung cancer reasons was taken from a Dutch study that collected data on heavy smokers aged 55 to 74 in the Netherlands (Du et al., 2020). The reason why the all-cause death rate is not based on the Danish population is that there is no smoking register in Denmark is because the Danish Health Data Authority does not hold this information about Danish citizens (Sundhetstyrelsen, 2022). The epidemiology from the Dutch high-risk population was seen as applicable to the same risk group in Denmark.

For the screening group that did not have lung cancer, the risk of dying was the same as the all-cause death above.

The next chance node in the screening pathway is whether the patient has lung cancer or not. The probabilities for developing lung cancer in the different stages were taken from a German CUA study on LDCT screening versus non-screening (Hofter et al., 2018). Hofter et al. (2018) used a Bayesian calibration method with the German Center for Cancer Registry Data data to estimate the transition probabilities. They set up a "Metropolis-Hastings algorithm with 50,000 runs and a "burn-in" of 10,000 runs" (p.190) which helped them identify the transition probabilities illustrated in the appendix. This thesis chose these transition probabilities because the German population is comparable to the Danish population and is closely situated in European high-income countries. Furthermore, no other studies outlined the lung cancer development and transition probabilities stated for the same NSCLC lung cancer stages, as much of the literature used simulation models, such as the Cancer Risk Management Model. It was also a preferred option to use these transition probabilities since the study also compared LDCT screening versus non-screening, and the diagnosis probabilities were easily transformed from the undiagnosed health states. The transition probabilities are illustrated in Table 9.

Table 9. Transition Probabilities Between Health States

Disease state	No apparent lung cancer	Stage I	Stage II	Stage IIIA	Stage IIIB	Stage IV	Pre-diagnosis mortality	Post-diagnosis mortality
No lung cancer	0.96509999	0.005	0.00000001	0	0	0	0.0299	0.0299
Stage I	0	0.37009999	0.3558	0.0328	0.00000001	0.0869	0.1544	0.08
Stage II	0	0	0.4939	0.248	0.006	0.129	0.1231	0.17
Stage IIIA	0	0	0	0.4772	0.2246	0.1455	0.1527	0.25
Stage IIIB	0	0	0	0	0.7811	0.0336	0.1853	0.49
Stage IV	0	0	0	0	0	0.7022	0.2978	0.69

Note. Hofer et al., 2018; Ekman et al., 2021

The following chance nodes consist of adherence versus non-adherence to the screening program for the screening group. This chance node is also related to a branch probability, as shown in Figure 7. These rates were taken from a study of cancer screening conducted in Denmark of people aged 50-74 by Kirkegaard (2015) where interviews were conducted for adherence to colorectal cancer screening programs. These numbers applied to this study since they explore publicly funded cancer screening programs in Denmark. Studies conducted in other countries have varied results of participation rates between 26% and 58%, according to the systematic review by Dressler et al. (2021). This participation rate might not seem so conservative to the reader. However, after talking to Bigaard (2022), a Danish project manager and head physician for breast cancer in

Denmark, specifically focusing on information related to screening (Aglund, 2018), this adherence rate was used with more confidence.

The following chance node illustrates the event and probability of getting diagnosed or not diagnosed with lung cancer through screening amongst the adherent group or through the current clinical pathway for the non-adherent group. Here the probabilities of getting diagnosed through LCST screening were taken from the Hofer et al. (2018) study as well. This was because Hofer et al. (2018) also explored the cost-effectiveness of the LDCT scan versus no screening, using the same cancer stages. Therefore, it was easy to apply the exact diagnosis probabilities used in their study. For the non-adherent group, the probabilities were taken from the same study. Listed below are the probabilities of diagnoses for each for LDCT screening versus the current clinical pathway.

Table 10. Diagnosis Probabilities for Current Pathway Versus LDCT Screening

Disease state	Diagnosis current pathway	Diagnosis LDCT screening
No lung cancer	0	0
Stage I	0.0246	0.4339
Stage II	0.027	0.4692
Stage IIIA	0.0811	0.691
Stage IIIB	0.5177	0.7709
Stage IV	0.6584	0.9781

Note. Hofer et al., 2018

The last node is the probability of dying or surviving amongst both the diagnosed and undiagnosed patient groups, for the screening group. As the healthy patients have already passed through the all cause mortality node, another mortality probability does not apply to them. For the patients who have developed lung cancer, there is however a possibility of dying of lung cancer. The probabilities of dying of lung cancer in the different undiagnosed lung cancer stages are taken from the Hofer et al. (2018) CUA article. The death probabilities for diagnosed patients come from a Danish study on epidemiology and survival outcomes between 2005 and 2015 for patients with NSCLC (Ekman et al., 2021). The study reported one-year survivability rates, ranging between an upper and lower band. Since Ekman et al. (2021) reported an overall 12% increase in survivability from 2005 to 2015, the mortality rate is calculated by taking one minus the probability of surviving, presented in Table 10 above. The probability of dying after diagnosis is the same for both the screening and current cohort.

The current lung cancer pathway is similar to the screening one, although it does not consist of an adherence or non-adherence stage. The probability of getting diagnosed through the current pathway is the same as for the non-adherent group in the screening cohort, i.e. the probabilities were taken from Hofer et al.'s (2018) study. The current non-screening pathway for detecting lung cancer is assumed to be similar between Germany and Denmark. Since the process moving forward from the diagnosis stage is the same for both groups moving on to treatment, aftercare, and palliative care, these stages are not illustrated in the decision tree in the results.

Stage 4: Implementing the Model

The decision tree, including probabilities and effects, is presented in the results section. This figure illustrates the risk groups' possible prognosis when altering the possible screening pathways and current clinical pathways and the associated QALYs for each branch.

Even though the decision tree is a good way to illustrate the different pathways, it has several limitations to it. It does not define time and events take place instantly and in parallel. The patients get screened, diagnosed, treated, or die instantly and in parallel for the screening group. The Markov model is a more suitable model for illustrating health interventions' costs and benefits over a long period. Therefore a Markov model will also be created for this thesis, presented in the next section.

4.3.1.2 Markov Model

The Markov model is a widely used model for EE which handles specific decision problems (Sonnenberg & Beck, 1993; Briggs & Sculpher, 1998). The Markov model is based on a series of states that patients can occupy at a given point of time and over discrete-time periods, called *cycles* (Drummond et al., 2015). The cycle should be limited to a period where the patient can only experience one event per cycle. The Markov model is also built on *Markov states* and *transition probabilities*.

The Markov states are the different health states that the patients can be in in the model. The states are mutually exclusive, and therefore a patient can only be in one event or Markov state per cycle (Drummond et al., 2015). The states should also be exhaustive so that the most critical health states for the disease are included in the model. A Markov state can also be absorbing, meaning that a patient cannot leave this stage, which happens when the patient, for example, dies.

Regarding the transition probabilities, these illustrate how patients move between health states. These are related to the Markov states so that the model shows how fast patients can move through the model over cycles. Transition probabilities can be the same throughout every cycle in the model, called *fixed transition probabilities*, also known as *Markov chains* (Drummond et al., 2015). These Markov models are time-invariant. Depending on the model structure, the transition probabilities can also vary over time, and these

Markov models are, therefore, *time-dependent*. Markov models can also differ and include stages of health improvements through the interventions or without improvement of health. The nature of the disease and interventions determine which transition probabilities are suitable for the developed Markov model. Furthermore, there are also different assumptions that the transition probabilities in the Markov states can depend on. One is the *memoryless* assumption that the transition probabilities depend on the current health state alone. Previous health status does not affect the transition probability in the state that the individual takes on in the current Markov state. The memoryless assumption is managed by building *tunnels* into the model (Drummond et al., 2015).

The Markov model is a *cohort model* and therefore calculates the average patient's outcomes and costs and does not consider variety between individual patients. Each state in the model usually has a cost and QALY associated with it, and a HRQoL weight is associated with the QALY measures. The expected costs and outcomes are calculated by identifying the average patient per health state during a specific time duration, in other words, the proportion of the patient cohort in a specific state at a point in time (Drummond et al., 2015). Calculations are typically done in a spreadsheet or similar software using a cohort-simulation method, producing a "Markov trace" illustrating how the proportion of the cohort moves between states over each cycle. Then the cohort proportion number for each state per cycle is weighted to relevant costs and HRQoL (Drummond et al., 2015). The total expected costs and effects for the whole period, including all cycles, are the sum of all expected costs and effects for all cycles. Discounting can also be implemented in the Markov model by adjusting expected costs and effects for each cycle by the chosen discount rate (Drummond et al., 2015), further explained in the *Discounting* section. One cohort simulation is created for each intervention option being evaluated to insert the expected costs and effects into the ICER equation.

Decision Problem

The specified question to be addressed is what the total expected costs and QALYs are for a 15 cycle time independent cohort Markov model? The costs are measured in Danish kroner (DKK), and effects are measured in QALYs. The Markov model is constructed in order to extrapolate costs and effects over time, because the literature suggests that the screening program gets effective after a few years after the implemented screening program. The objective is to gather cost and QALY results for the LDCT screening program versus the current pathways to calculate an ICER and determine the screening program's cost-effectiveness to its comparator.

Model Boundaries

In terms of explored disease, intervention options compared, and cohort and risk group, the model follows the inclusion criteria explained in the *Model Scope* section. Furthermore, the inclusion of cost and QALY data are explained in the *Cost* and *Benefits* sections. The Markov model is further narrowed into a time horizon of 15

time-independent cycle years. The post-diagnosis progression stages are not included, nor the possibility of false positive rates.

Conceptualizing the Decision Model

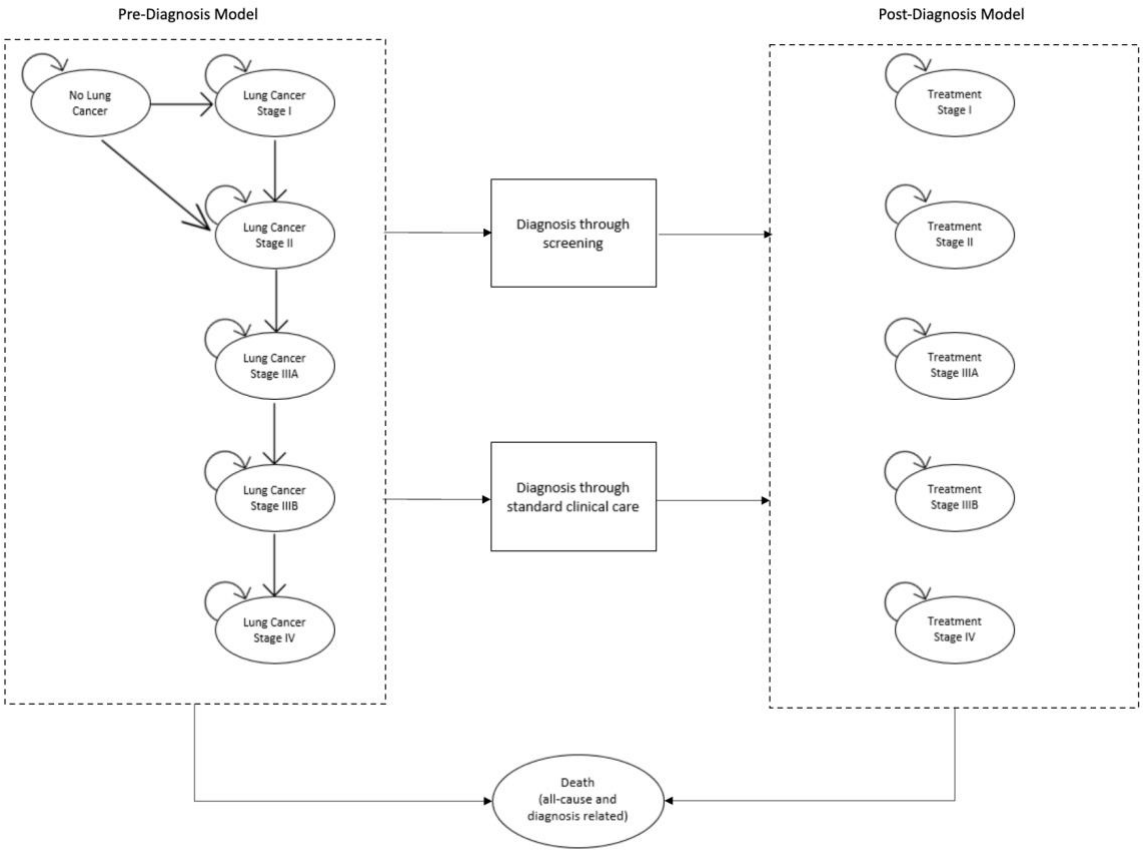
Two cohort simulations are created for the two compared interventions to illustrate how individuals and patients move through the Markov states over time using a set of transition probabilities. The Markov states in the model follow the definition by the International Association for the Study of Lung Cancer's lung cancer stages defined in the *Background* section. The lung cancer stages are Stage I, Stage II, Stage IIIA, Stage IIIB, and Stage IV. There was no need to account for the interaction between individuals since cancer is a non-communicable disease. The model also includes diagnosis stages and absorbing death states for lung cancer stages.

The cycle length and number of cycles were decided based on the characteristics of the disease, cohort group, screening intervention, and current CUA literature. The cycle length in the model is one year because it is the most used cycle length, following the identified EEs for lung cancer screening studies gathered in a meta-study from Peters et al. (2021). As previously mentioned, the time horizon is 15 cycles. Different EEs have reported time horizons for Markov models between 10-45 years but 15 years is the most common time horizon (Peters et al., 2021). Since it is rare to screen the same person for 15 cycle years, the results in this thesis will also present ICERs based on shorter periods in the appendix.

The input values for the natural history part of the Markov model were identified by assuming that one could simulate one cohort Markov model for the current pathway cohort for 30 cycle years. The output rates from each cancer stage in this Markov model will be used to calculate the input values in the main cohort simulations, used for the results in this study. The rates are multiplied but the total number at risk (106,041) to arrive at the starting distribution of the natural history part of the model for each cancer stage. Since there is no screening program for lung cancer in Denmark today, the input values will be identified using a cohort simulation from the current diagnostic pathway, excluding screening. The starting distribution for diagnosed patients is assumed to be zero. The starting distribution for each lung cancer stage is presented in the results section.

The Markov model type used in both the cohort simulations is fixed time-invariant without improvement (Markov chain) and with absorbing death states. Therefore, the cohort simulations accept the assumptions that patients' health cannot improve due to the nature of the disease progression, further explained below and illustrated in Figure 6.

Figure 6. Fixed Time-Invariant Markov Chain



Note. Hofer et al., 2018; Du et al., 2020

Both of the cohort simulations use the same transition probabilities between Markov states. These are the same as the health states used in the decision tree. The patients cannot go back from a poorly state to an improved health state, with a zero probability of moving from, for instance Stage I to no lung cancer as illustrated in Figure 6. This model choice is connected to the nature of the disease as lung cancer will continue to spread without treatment.

The diagnosis stage can only happen once in the model but is not an absorbing state. The diagnosis probabilities are the same as in the decision tree, illustrated in Table 9. In the illustrated Markov model, the assumption is that once a patient is diagnosed it moves to the corresponding treatment stage where they stay until they die. In real life patients would move into a treatment stage with the possibility to progress to other cancer stages or enter an aftercare stage or palliative care stage. Due to limited resources in time and the fact that both cohorts move through these stages identically once diagnosed, these stages were not outlined in detail in the model.

The death state is absorbing, therefore, the patients cannot move from the death state to another stage in the model and instead leave the model. The mortality rates for all-cause death reasons, undiagnosed lung cancer patients, and diagnosed patients are the same as in the decision tree.

Implementing the Model

Having formulated the Markov states and the probabilities of moving between states, costs and effects should be assigned to the different stages. Each cycle time has costs and effects associated with the different Markov states. To calculate the expected values, the highest QALY values are assigned to the Markov state "no lung cancer" and the lowest (zero QALYs) to the different death states. In regards to costs, the different lung cancer diagnosis stages are associated with the average treatment cost per stage. Both costs and QALYs are calculated as totals for each cycle and presented in non-discounted and discounted results. A total of all 15 cycles together is also presented in the result, used to calculate the base case ICER. The result of the Markov model is presented in the result section, and a detailed version of the cohort simulations can be found in the supplementary excel files. As stated throughout the text, several assumptions were made when creating and structuring the Markov model, summarized and presented below.

Table 11. Summary of Assumptions in Markov Model

Event	**Assumption**	**Outcome/Effect**
Markov model structure, Memoryless	Future events only depend on the current stage and not events occurring before the current stage.	
Starting distribution for health states	The probability of the cohort being in the different starting stages of lung cancer or no lung cancer can be calculated based on running a Markov model simulation for the current cohort for 30 cycles and seeing what the output values are.	The output rate of individuals in each cancer stage or no lung cancer, can be used for the input distribution in the Markov model used to calculate the ICER.
Cohort group	No people enter the model but people leave the model through the absorbing death state.	The amount of people after 15 years will be lower than in the beginning of the model since individuals leave but no individuals enter the model.
The probabilities are fixed	The probabilities of events stays the same for each cycle, over the whole time horizon.	For instance, patients have the same risk of dying though the whole model, regardless of age or duration they have had cancer.
Adherence	The adherence rate for a lung cancer screening program would be 58% The screening adherence stays the same over 15 years	Number of people that would adhere to a screening program once implemented in Denmark. Same probability of people getting screened in the first cycles like the last cycles.
Mortality	All-cause mortality does not differ between the LDCT and current pathway groups. The death probability is the same for all patients in the same diagnosed cancer stage and stable throughout the model. A person can only die once in the model. The risk of dying once diagnosed with lung cancer remains stable throughout the model, with a one-year mortality rate. Death after diagnosis differs from probability of dying before diagnosis	Affect QALY outcomes, death equals to zero QALYs. Affects cost outcomes, cost for dead patients is zero.
Diagnosis	A person can only get diagnosed once in the model.	No double counting of diagnosed people.

	A person will get diagnosed through the screening program after the mortality and the standard clinical care diagnostic probability is applied.	
False-positive rates	All patients are correctly diagnosed through screening.	There are no wrongly diagnosed patients in the model, and therefore no costs or effects representing false-positives.
Cost	A dead person does not cost anything if not screened. Costs will be the same for all patients in the same lung cancer stage.	Costs for lung cancer treatment remain stable once diagnosed. Costs of disease progression are not accounted for once diagnosed.
QALYs	QALYs remains stable in the whole model for each state, and is not adjusted for age, gender, or other events.	QALYs are fixed for each health state.
No other events	The patients are only at risk of dying, getting lung cancer, getting diagnosed with lung cancer, or staying healthy over time. No other events or diseases can occur to the patients.	QALY and costs in the model can only be affected by death, diagnosis, or disease progression.
Threshold	The Swedish CET can be applied to a Danish context.	Determines the cost-effectiveness of the LDCT screening.

In conclusion, this EE conducts a time-invariant Markov model without improvement and with an absorbing death state. It uses one-year cycles for a 15-year time horizon and accepts the above assumptions. The following section will explain the cost and effect data used in the decision models to calculate the expected cost and QALYs.

4.4 Perspectives

Once the model is created, one must decide which perspectives to follow when identifying the costs and benefits data (Byford & Raftery, 1998). The perspectives highlight the different stakeholders affected by an EE, dictating which costs and consequences should be included and how they are measured and valued within a CUA (Drummond et al., 2015). This chapter examines the economic impact of lung cancer from a healthcare payer perspective. The benefits or QALYs are measured through the standard gamble method and both costs and QALYs will be discounted with appropriate discount rates.

4.4.1 Costs

Several different perspectives can be followed for identifying cost data within EEs, with the choice of cost perspective to advise different types of decision-makers in health care (Drummond et al., 2015). The decision-makers in healthcare can extend beyond the direct beneficiaries of such interventions and can encompass the patients and clinicians, reimbursement authorities, national health ministries, healthcare providers, and other aspects valued by society, such as education, taxation, and pensions.

The different cost perspectives reflect the decision-makers and include the societal; healthcare sector (provider perspective); public sector; and private sector (Drummond et al., 2015). The cost perspectives will differ depending on the country and the healthcare model, such as the Beveridge model in Denmark. Specifying the cost perspective is essential as the choice affects the outcome of the result. It needs to target its intended audience, where different costs can hold relevance to one decision-maker but not to others (Kristensen & Sigmund, 2008). The payer perspective is the chosen perspective for this thesis.

Payer Perspective

The *payer perspective* within the Danish context refers to the Ministry of Health, the primary audience of this thesis, and the governmental body acting as decision-makers for health interventions and policies (Kristensen & Sigmund, 2008). The payer perspective focuses on direct costs associated with delivering an intervention, including the costs of the hospital or primary healthcare sectors associated with the resources for the intervention, treatment, or service (Drummond et al., 2015). *Direct costs* associated with lung cancer treatment include health personnel, medicine, capital equipment, overhead costs, inpatient stays, and outpatient visits (Drummond et al., 2015). Direct costs of the primary healthcare sector can include GP consultations and specialists, allied health, and medications (Drummond et al., 2015). Because of this perspective choice, the costs that fall onto the patient or their carers have been excluded.

Societal Perspective

The *societal perspective* offers a much broader understanding of the cost and effects of interventions without bias. The societal perspective includes all economic agents consumed for an intervention and the indirect costs, and consumption individuals must expend to receive an intervention or service (Drummond et al., 2015). Therefore, an EE that follows the societal perspective should include all costs incurred by society, including direct costs to the patient and family, time to access care, indirect costs, future costs, productivity losses and gains, capital, and shared costs (Fakhri et al., 2017). It has been argued that all CUAs should adopt a societal perspective to incorporate all costs. Drummond et al. (2015) states that EEs in health care should consider the societal viewpoint where feasible. However, other perspectives should be utilized where analytical difficulties preclude total measurement and valuation of all monetary costs and consequences. The societal perspective is

not used in this thesis as the direct costs borne by patients, and their carers could not be accurately estimated within the available literature. However, it is hypothesized by Drummond et al. (2015) that the inclusion of patient-borne costs will likely increase the ICER and place an additional burden upon patients.

The societal perspective includes the *direct costs* by all healthcare services and providers and the costs absorbed by the patient, such as time used to access care, transport costs, and carers' time. To calculate these costs, the market price is applied where able (Drummond et al., 2015). For costs unable to be estimated due to an absence of markets, for example, patient and carer time, hypothetical estimations are applied (Drummond et al., 2015). A common numeraire is placed on these non-health additions to provide a standardized quantifiable value, allowing for aggregation of costs to understand the net consumable impact on an overall EE of an intervention (Drummond et al., 2015).

Indirect costs are those borne which are unrelated to undertaking an intervention or service (Drummond et al., 2015). These costs can impact the broader economy and are the costs that are external to the patients, the intervention, or those involved in the screening process (Drummond et al., 2015). However, these costs were unable to be reliably estimated from the literature. These costs are valued by society and may include treating benign findings in the screening process, the psychological consequences of a false positive diagnosis, patients accessing resources to assist with smoking cessation, and loss of future income. It can also include the cost of returning someone to a complete state of health or the disutility someone faces once they receive a cancer diagnosis (Drummond et al., 2015).

Future costs are defined as the costs arising from extending individuals' lives through intervention and all the costs borne in the life years gained (Drummond et al., 2015). Future costs are typically separated into *medical costs* (applicable for societal and healthcare perspectives) and *non-medical costs* (relevant for societal perspectives) (Kellerborg et al., 2020). Further divestment of medical costs can include *related* and *unrelated costs* (Drummond et al., 2015). These include ongoing medical appointments for lung cancer or homecare assistance for post-diagnosis disutility, respectively (Kellerborg et al., 2020). Discounting must be applied to future costs to account for changes in value over time and to calculate the present value of future costs (Drummond et al., 2015). The discount rate will be discussed further in this thesis in section 3.3.2.3.

Determining productivity changes is considered in societal costs and estimates changes in productivity and the cost this has to society. There are two main methods to estimate productivity costs, the *friction-cost method* (FCM) and the *human capital method* (HCM). The HCM method estimates the gross earnings of those in employment, including the cost of replacing the role of the individual, be it in the workplace or the home (Drummond et al., 2015). Koopmanschap et al. (1995) have also estimated productivity losses through the FCM. This method specifies *"[...] is that the amount of production lost due to disease depends on organizations' time to restore the initial production level. This friction period is likely to differ by location,*

industry, firm, and category of worker" (Drummond, 2015, p. 247). The HCM method can often overestimate costs to society and does not include the adjustments made by employers to compensate for employee absence or disutility, whereas economic evaluations comparing the FCM and HCM have produced significantly lower values when using the FCM (Drummond et al., 2015). Neither method includes the loss of productivity when a worker remains in employment and is often referred to as "*presenteeism*." However, productivity losses can lead to equity considerations for unemployed participants due to age, illness, or personal choice (Drummond et al., 2015). For this thesis, the screening cohort has participants within retirement age. Including the productivity changes in this cohort may present biases for those who are not employed due to retirement or other reasons.

Capital costs refer to investments at a single point in time in the intervention used for different interventions (Drummond et al., 2015). In order to allocate these costs to goods that are used directly in the screening program, the costs for establishing and running the program must be identified and included, affecting the ICER. These costs would relate to establishing an adequate volume of CT scanners in Denmark to facilitate scanning the screening population, employing radiographers to conduct the scan, and radiologists to review and make a diagnosis based on the imaging, with the cost allocated depending on the frequency and duration of scans performed. The cost per scan is included in this thesis in section 3.3.2.1. However, the upfront costs of establishing a lung cancer screening program are not included, as these costs would be shared with other areas of the Danish healthcare service. *Shared costs* are the overhead costs associated with the resources needed for the screening program but will also be utilized by other parts of the healthcare network. These costs include the use of central service, including cleaning, overhead laboratory costs, disposables, and utilities, and have not been estimated for this thesis.

Cost Overview

According to Drummond et al. (2015), the payer perspective is the most common cost perspective to assess healthcare programs and interventions. Meta-studies examining previous CUAs and CEAs have shown that 74% adopt a payer perspective, and 67% of governmental guidelines recommend the healthcare sector or payer perspective (Kim et al., 2020). The motivation behind this choice spurred from both the data available within the thesis' delimitations and the universal healthcare model in Denmark. Cost data was reliably sourced from a Danish epidemiologist, who provided costs based on the Danish national registries. The data required to use an alternate perspective could not be reliably estimated from the available literature.

Cost Data Collection

Including costs in EE consists of three steps, (1) identification, (2) measurements, and (3) valuation (Serena, 2021). Firstly, the resources required to conduct an EE should be identified concerning the chosen perspective

(Kristensen & Sigmund, 2008). The various methods used to help identify associated costs can be done from pilot studies, expert opinions, or modeling the possible disease pathways and therapeutic options through a decision tree (Kristensen & Sigmund, 2008). The direct resources identified for this thesis are related to the primary and acute healthcare sector or payer perspective. These included the price of undertaking a LDCT scan for a screening program, the treatment of lung cancer, and the costs of the current standard clinical pathway.

Measuring resource consumption can be done by collecting prospective and retrospective patient-specific or deterministic data (Kristensen & Sigmund, 2008). Prospective data collection is patient-specific and is usually measured within clinical trials (Kristensen & Sigmund, 2008). Retrospective data collection is when data is collected after events, often through questionnaires or patient records, measuring the consumption of a specific service (Kristensen & Sigmund, 2008). Deterministic data represents standard or average treatment costs and can be collected via prospective or retrospective methods (Kristensen & Sigmund, 2008). Expressing cost should be in monetary value as opportunity costs or costs relating to forgoing another alternative. This thesis presents the monetary value applied to the LCSP intervention, as the resources used to facilitate this program cannot be allocated elsewhere. Finally, when costs are identified and measured as price per quantity, they are valued in the form of unit costs. The price must correspond to the opportunity cost, often inflating the value of a resource, as the demand for the resource is lower than the demand (Kristensen & Sigmund, 2008). The health outcomes can be expressed as monetary or non-monetary, depending on the outcome. This thesis uses the Danish kroner (DKK) to monetize the costs identified.

The direct costs were sourced from persons Dr. Zaigham Saghir and Professor Anders Green (2022). Dr. Saghir, a clinical associate professor in lung cancer diagnostics, is the key person responsible for drafting and submitting a lung cancer screening proposal from the Danish Lung Cancer Group to the Ministry of Health (Danish Lung Cancer Group & Saghir, 2021). The submission is currently (2022) under review by Sundhedsstyrelsen, the National Board of Health. The proposal uses costs created by Professor Anders Green for the 2011-2012 treatment of non-small cell lung cancer. Anders Green, a professor of epidemiology at the University of Southern Denmark, was contacted directly about supplying more recent non-small cell lung cancer costs and assisted in providing average total costs for lung cancer in Denmark for 2013-2015. Professor Green provided mix-case costs, giving the cost for each category of case based on deterministic measuring methods (Drummond et at., 2015). The cost matrices were produced using the Diagnosis-Related group database (DRG-DAGS), the Danish Cancer Registry, and Danish National Patient Register.

As previously mentioned, The focus of this EE is on NSCLC, as it represents 85-90% of all lung cancers in Denmark. As treatment pathways differ widely between NSCLC and other lung cancers, the treatment probabilities and costs will reflect that of NSCLC. Including treatments for all lung cancer types would involve

creating additional Markov models as small-cell lung cancer (SCLC) treatment differs significantly from NSCLC (Gadgeel et al., 2012). The majority of other EEs and feasibility studies for LCSP focus on NSCLC, however, this does not exclude other cancers from being incidentally detected during the screening program (Goffin et al., 2015; Hofer et al., 2018; Pedersen et al., 2017; Snowsill et al., 2018).

Professor Green identified the total annual costs of primary NSCLC via the DRG code and divided this by the annual incidence. The costs were further stratified by both stages and the time horizons of <180 days and ≥180 days, displayed below in Table 12. As this thesis aims to determine whether introducing a LCSP to Denmark is overall cost-effective, the costs of NSCLC treatment for <180 days and ≥180 days were combined to present total treatment costs. These costs are applied to all individuals diagnosed with NSCLC in the intervention and comparator groups.

Table 12. Total Lung Cancer Treatment Costs in Denmark (2015)

Total Lung Cancer Treatment Costs (2015)						
Lung Cancer Stage	- Resection - Oncology		- Resection + Oncology		+ Resection +/- Oncology	
I	DKK	267,123.70	DKK	370,657.27	DKK	225,823.33
II	DKK	272,161.19	DKK	416,373.43	DKK	190,382.63
IIIA	DKK	395,397.13	DKK	457,490.02	DKK	282,022.54
IIIB	DKK	661,166.22	DKK	497,985.81	DKK	249,054.61
IV	DKK	852,086.42	DKK	671,055.08	DKK	386,532.17

Note. Danish Lung Cancer Group & Saghir, 2021

To further specify the costs for lung cancer, the weighted cost of treatment was established per lung cancer stage. These costs were created using the above Table 12, then multiplying each cost by the treatment probabilities for clinical care by lung cancer outlined in section 2.3.2. Inflation has been considered, with costs adjusted to reflect the Consumer Price Index (CPI) changes from 2015 to 2022 (Statistics Denmark, n.d.). The CPI is used to measure inflation and measures the development of consumer goods and services (Statistics Denmark, n.d.), which has caused a cost increase of 8% from 2015 to January 2022, reflected in the current costs in Table 13.

Table 13.Weighted Lung Cancer Treatment Costs

Weighted Lung Cancer Treatment Costs (2022)		
Lung Cancer Stage	Weighted cost	
I	DKK	286,126.37
II	DKK	280,090.35
IIIA	DKK	430,915.23
IIIB	DKK	548,582.64
IV	DKK	765,492.05

Note. Danish Lung Cancer Group & Saghir, 2021

Cost of a Lung Cancer Screening Program

As the payer perspective has been chosen, costs absorbed by the Danish Ministry of Health relating to lung cancer screening must be identified. The costs of the LCSP were sourced from the article "Direct and indirect healthcare costs of lung cancer LDCT screening in Denmark: a registry study" (Jensen et al., 2020). The cost was measured to include recruitment of participants, use of the physical technology, and the associated staff resources, including a radiologist, to review and comment on scans. The total cost of introducing a LDCT was calculated at €238 per scan per participant (Jensen et al., 2020). This CPI was adjusted for inflation from 2020 to 2022, equaling €247.86. This price was then converted to 1844 DKK using Danmarks Nationalbank (Denmark's National Bank, 2022). The cost associated with additional imaging or procedures to confirm a cancer diagnosis was not included, as these costs could not be reliably estimated within the literature.

Costs of the Comparator

Calculating the cost of the comparator is vital in determining the delta between the intervention group and the comparator. The current pathway for lung cancer diagnosis in Denmark is through symptomatic patient presentation to their GP or an acute care setting. Symptomatic presentations leading to diagnosis will occur on an ad-hoc basis and not in a timed or coordinated manner as with a screening program. As the costs for confirming diagnosis have not been included in the intervention group, these costs were also omitted from the comparator group. There will be no changes or disruptions to the comparator group, so a cost of €0 is applied to the comparator group. The post-diagnosis costs are then the same as for det LDCT group.

False Positive Costs

False positive costs were not included in this CUA, despite the Danish payer's ownership of these costs. False positive costs are the costs incurred for a participant requiring further diagnostic investigations for an abnormality eventuated as benign (Hammer et al., 2022). False positives can arise, for example, from damage

or congestion in the lungs from recent infections, with further diagnostic investigations potentially including increased frequency of scanning via LDCT, biomarker investigations, bronchoscopies, and biopsies. False positives occurred in a small proportion of individuals in all RCTs reviewed. However, the extent to which the false positives were detected is inconsistent across the literature. Therefore, the costs were often omitted and not included in this thesis.

This thesis has focused on the Danish payer perspective when introducing a LCSP due to data availability and accuracy. However, a more detailed and potentially targeted CUA could be achieved using a societal perspective. Having this in mind, it is difficult to capture all aspects of value in economic analysis, and the values chosen may hold different worth depending on the audience. The results and discussion will reflect the provider perspective chosen and should be considered by the reader.

4.4.2 Benefits

Some of the benefits obtained in EE can be seen as changes to health-related quality of life or an extension of life with poor health, which can be measured in QALYs and disability-adjusted life years (DALYs) (Drummond et al., 2015). The outcome in focus for this thesis is QALYs. They are a generic measurement of benefits widely used, acknowledging that health technologies can impact the mortality and morbidity of those consuming the technology (Drummond et al., 2015; Kristensen & Sigmund, 2008).

QALYs are defined as the measurement of both the quality and quantity of life due to health interventions (Salomon, 2017). QALYs can encompass every patient population, disease, and intervention to conduct comparisons across the healthcare sector (Kristensen & Sigmund, 2008). They allow for quantification and comparison of disease states through a standard scale for years lived in full health (Salomon, 2017). The primary motivation for using QALYs as the unit of measurement is that QALYs were available within the literature. The CUA articles on LCSPs use QALYs as their standard unit of measurement and not disability-adjusted life years (DALY), allowing for comparisons across studies (Peters et al., 2022).

QALYs are calculated by quality-adjusting each life-year gained from an intervention (Drummond et al., 2015). QALYs, also referred to as health utilities, are weighted from 0 to 1 and, in some circumstances, can fall below 0 for states worse than death or where interventions reduce the quality of life (Drummond et al., 2015). Between the indices 0 and 1, there are varying states of health and disability which will all have a QALY of <1 (Kristensen & Sigmund, 2008). QALYs measure the quality and quantity of life gained from interventions, including the gains from reduced mortality and morbidity (Drummond et al., 2015).

DALYs are the loss measurements of the equivalent of one year of full health (World Health Organization, n.d.). As defined by the WHO, "DALYs for a disease or health condition is the sum of the years of life lost due to premature mortality and the years lived with a disability due to prevalent cases of the disease or health

condition in a population" (World Health Organization, n.d.). DALYs are gathered through trade-off scores and do not use associated age weights (Drummond et al., 2015). Due to other CUAs referenced in this study not using DALYs as their outcome, this thesis has chosen the QALY approach for measuring benefits.

Methods to Gather Quality-Adjusted Life-Years Data

QALY data must be gathered and derived through validated and reliable methods and include using standard gamble, visual analog scales (VAS), or time trade-off (TTO) (Drummond et al., 2015). Standard gamble, which is used in this thesis, involves risk where patients are asked to prefer staying in a specific health state or returning to perfect health with a percentile risk of death (Drummond et al., 2015). As many respondents cannot relate to the chronic health state, visual aids are used to support decision-making (Drummond et al., 2015). This method uses uncertainty as a gauge for guiding decision-makers and can generally produce higher scores than other methods, such as the TTO or VAS (Drummond et al., 2015).

VAS is a simple method of gathering QALY data and is widely used in psychometric and health research (Drummond et al., 2015). VAS involves utilizing a visual scale with endpoints 0 (worst-imaginable health state) and 100 (best-imaginable health state), where participants are asked to rank their current health state before and after an intervention (Drummond et al., 2015). Administering these tests produces reliable results when endpoints are unambiguous, and results can be compared over time and with other patients from the same population (Drummond et al., 2015). A significant criticism of VAS is that it does not have any underlying economic theoretical framework (Johannesson et al., 1996). Also, using the VAS method does not present a choice, so it is not possible to trade-off scenarios and only provides preference. Moreover, it is viewed that "choiceless" techniques for data collection are not based on economic theory (Johannesson et al., 1996).

The TTO method was developed for specific use in healthcare and asks individuals if they would rather live the rest of their lives in certain health states or live in full health for a shorter period. This process is repeated until no distinction can be made between the two stages (Drummond & McGuire, 2001, Whitehead & Ali, 2010). However, several criticisms of the TTO method exist. The TTO results often have to be adjusted before becoming QALYs, or utilities and reflecting trade-offs between living in certain health states and death. Also, if illnesses considered are shortly followed by death, this can distort the outcomes (Drummond et al., 2015). It is also shown in respondents who do not believe it is possible to return to full health after an illness.

Quality-Adjusted Life-Years Used

Due to the lack of validated QALY data for the Danish population, the utilities in this thesis are taken directly from the study by Hofer et al. (2018), which is reflective of the German population. It is acknowledged that QALYs can vary widely among lung cancer patients. Hence Hofer et al. (2018) referenced their utilities from the pooled quality of life studies taken from the meta-analysis by Sturza (2010). The utilities obtained by Sturza

(2010) were gathered via the standard gamble method, with the patients as the respondents and NSCLC as the disease scaled from death to perfect health. The starting QALY of no lung cancer was for people aged 55 and 75 years in Germany to maintain consistency with using German lung cancer utilities (Hofer et al., (2018). An assumption was made that the QALYs assigned for patients with undetected lung cancer remained the same as those diagnosed with lung cancer, as it is difficult to determine the QALY weight assigned to a person with undiagnosed cancer. Other literature was researched for their QALY weights, however, Hofer et al. (2018) was chosen due to the geographical proximity to Denmark, as well as similarities across the Danish population.

Additionally, the QALY weights have to align with the cost data, accounting for each lung cancer stage explored in this thesis. Some CUA studies only presented QALY weights on stages I, II, III, and IV (Goffin et al., 2015; Field et al., 2016). However, due to treatment and mortality rates ranging widely in stages IIIA and IIIB, the researchers decided to include these QALYs within our model. Table 14 outlines the QALYs used in this thesis for all states.

Table 14. Health States with Associated Utility Weights

Health State	Utility (QALY)
No diagnosed lung cancer	0.891
Diagnosed Stage I	0.825
Diagnosed Stage II	0.825
Diagnosed Stage IIIA	0.772
Diagnosed Stage IIIB	0.573
Diagnosed Stage IV	0.573
Death	0

Note. Hofer et al., 2018

In summary, QALY weights for lung cancer do not yet exist within a Danish context. To circumvent this, QALYs were obtained from the German study by Hofer et al. (2018). These QALYs were sourced from a metastudy by Sturza (2010), examining QALYs using the standard gamble method. This source was chosen due to its proximity to Denmark, both geographically and in population, and corresponding with this thesis'

cost data. The following section will outline the choice of discounting perspective, followed by the sensitivity analysis.

4.4.3 Discounting

Cost and benefit discounting is the process that adjusts for future costs and benefits of a healthcare intervention to present-day value (Severens & Milne, 2004). As discounting can influence the outcomes of an EE, this section will outline the rationale for discounting, the rates applied for both the costs and benefits associated with a LCSP in Denmark and how they will be accounted for in the economic analysis. The purpose of discounting future costs and benefits is to account for the impact of time preference and adjusts the value of future benefits and costs to that of present-day value (Drummond et al., 2015). Measuring discounting for both costs and benefits can be shown as (1/1+D)n, where *(D)* is the discount rate and *(n)* is the year in the future the discount is applied (Severens & Milne, 2004).

Discounting Costs

The principle for discounting future costs is that money has greater worth in the present than in the future if it is spent and not invested in other sectors of the economy at a positive rate of return (Drummond et al., 2015). This can be due to:

1. Individuals think the future is uncertain (risk of, for instance, death),
2. Individuals prefer consumption sooner than later,
3. Individuals assume their incomes will increase over time to consume more in the future.

The discount rate for the costs of an intervention can be performed through two methods, the social time preference, and the social opportunity cost. The social time preference approach is used in this thesis and refers to the positive rate of time preference, where one benefits from receiving an intervention earlier than later (Drummond et al., 2015). Applying the social discount rate factors the impacts occurring in different years from an intervention, with lower rates favoring interventions that present more significant benefits in the future and higher rates indicating immediate benefits (Moore & Vining, 2018).

The other method for applying discount rates to benefits is the social opportunity cost of capital, which uses societal perspectives and is the method that is most commonly used in Denmark for CBAs. However, as the social opportunity cost is used within societal perspective CUAs, it is not utilized for this thesis. The societal perspective takes the opportunity costs of the intervention in projects where capital investment is required (Drummond et al., 2015). If investments were made in a screening program, this money has not been invested

at a positive rate of return and earning interest, meaning that investments made now would be worthless (Drummond et al., 2015). This can lead to depreciation of opportunity costs, and therefore investments should be made where the best investment can be made.

Discounting Benefits

Discounting health benefits is based on "positive time preference" in that those receiving an intervention prefer immediate benefits over future benefits and will gain benefits in the interim time (Severens & Milne, 2004). The positive time preference means benefits received sooner will be of higher value than those received in the future, hence future benefits are discounted to account for this (Severens & Milne, 2004). Positive time preference is a valuation approach and is elicited from either a stated preference (SP) or a revealed preference (RP) (Abdullah et al., 2011). SP uses hypothetical situations to elicit preferences and values through survey-based techniques (Abdullah et al., 2011). RP uses the consumption patterns of an individual to learn about their preferences and holds high reliability and face validity as it portrays the world as it currently is (Abdullah et al., 2011).

Discount Rate

The Danish Ministry of Finance sets a cost and benefit discount rate of 4%, used within this EE (Finansministeriet, n.d.). The non-discounted costs for each cycle in the Markov model must first be established to determine the discounted costs rate. In order to discount, the total non-discounted costs and QALYs are divided by the discounted rate of 4% to the power of the number of years (n) the costs refer to, or $(1/1 + 0.04)^n$.

There are conflicting ideas surrounding discounting costs at the same rate as benefits, and uncertainty around the future can lead to criticism of current discount rates (Drummond et al., 2015). As in Denmark, discounting at the same rate follows the "consistency" argument, assuming that life-years and cost relationships are independent of time (Severens & Milne, 2004). In situations where health will become more valuable over time, a differential discount rate can be applied (Attema et al., 2018). However, discounting health outcomes at a lower rate, as in the Netherlands, can lead to the Keeler-Cretin Paradox, which shows that programs are more cost-effective if their introduction is delayed (Severens & Milne, 2004). It is agreed that it is in society's best interest to invest in health. However, discounting benefits at a lower rate than costs can lead to indefinite deferral of spending on healthcare, essentially providing no opportunity for healthcare benefit gains to be made. Additionally, Gravelle and Smith (2001) argue that discounting QALYs removes the possibility of future utility gains that an intervention may provide. Calculating the discount rate is nearly identical to discounting for costs and employs the same equation but using the number of individuals in that health state multiplied by QALYs.

This CUA will adopt the discount rate of 4% for costs and benefits specified by the Danish Ministry of Finance and set for social time preference. The economic model will be constructed according to the choice of perspective, with further sensitivity analysis applied to the discounting rates to determine their impact on the economic-utilization.

4.5 Sensitivity Analysis

Sensitivity analysis is used in EEs to assess how varied inputs could impact the results (Drummond et al., 2015). As no intervention can be tested on a whole population, sensitivity testing is essential for any EE. It can determine a model's robustness by investigating the conclusions when assumptions of a model change. This section will outline two methods of conducting a sensitivity analysis, *deterministic sensitivity analysis* (DSA) and *probabilistic sensitivity analysis* (PSA) (Drummond et al., 2015). The sensitivity methods utilized for this EE will be explored. The justifications behind the decisions of tested parameters will be explained, with all simulations for this thesis conducted in Microsoft Excel.

4.5.1 Deterministic Sensitivity Analysis

A DSA is used to test the robustness of an EE and evaluate uncertainty and can be performed through a single or two-way approach (Drummond et al., 2015). This EE will perform a series of single- and two-way sensitivity analysis to test the robustness of assumptions and choices in the model. A model is considered robust when the output accuracy is not significantly altered from the baseline under alternate conditions (Drummond et al., 2015). The main assumptions within the model have been tested, with the sensitivity ranges extracted from EE literature. Table 15 displays the parameters with the current assumptions, base case ICER value, and upper and lower bounds.

4.5.1.1 One-Way Deterministic Sensitivity Analysis

A one-way DSA is the most straightforward sensitivity analysis, involving changing single values for the input parameters while the others remain unchanged (Drummond et al., 2015). One-way sensitivity analyses can explain the quantitative relationships between inputs and outputs within a model as they should display predictable results. It also allows for exploring the structural integrity of an economic model (Drummond et al., 2015). A one-way analysis will show the sensitivity of outputs to particular input parameter changes. However, it cannot indicate which parameters contribute to decision uncertainty (Drummond et al., 2015).

DSAs include inputting "extreme yet plausible" upper and lower bounds of values (Drummond et al., 2015, p.394). Testing these values can determine the results of best-case and worst-case scenarios, and parameter uncertainty. A parameter can be considered sensitive when the baseline output changes after its variation

(Drummond et al., 2015). It can be beneficial in helping determine the values needed to produce sufficient changes to costs and effects. Challenges here can be found with uncertainty in estimating the parameters of interest, identifying the upper and lower bounds, and an inability to justify the parameters taken can risk producing misleading results and second order uncertainty (Drummond et al., 2015). The result of the single-way DSA will be presented in a *Tornado Diagram.* A tornado diagram is able to determine which parameters have the most influence on a model. The parameters tested through one-way sensitivity analysis in this thesis are listed below.

Adherence

Testing the sensitivity of adherence to a screening program is essential as adherence could affect the cost-effectiveness of the intervention. Inadequate participation could yield no health benefits to the targeted population (Baccolini et al., 2022). However, increased uptake of screening services can also inflate costs dramatically; hence determining the impact of adherence should be explored. The assumption is challenged in adding the upper and lower bound limits of +/- 50% to the current adherence rate in 25% increments. This threshold was used in the reference paper by Hofer et al. (2017) and can be seen in other economic analyses (Snowsill et al., 2018; Du et al., 2020).

Disease Transition Probabilities

Lung cancer disease progression within this EE is represented through transition probabilities obtained from Hofer et al. (2018) paper, motivated in section 3.2.3.1. Because of the difficulties in finding disease progression probabilities in the literature, the used transition probabilities have been adjusted to present varying stages of disease progression. The risk of cancer progression was altered to doubling and halving as the upper and lower bounds. The sensitivity will explore the impact of disease progression only in the pre-diagnosis stages, as progression in the aftercare and palliative care have not been included in this EE.

Diagnosis Sensitivity

The sensitivities of the diagnosis through standard clinical pathway and LDCT scanning will be adjusted. Testing the sensitivity of the standard clinical care pathway will determine whether improving the diagnosis in current clinical workflows will impact the outcome. These parameters can be tested to see whether investments should be made in the current clinical settings or whether a focus on innovations or alternative methods should be investigated. The value was adjusted by +/-50% to explore the most significant sensitivity changes within the model. The sensitivity of LDCT scanners is adjusted by an upper and lower bound of 20%. There are two reasons behind these parameter variations. Firstly, it is estimated by the Exeter Test Group and Health Economics Group (2022), that lung cancers diagnosed at stage IV by screening detection are overestimated, while underestimating earlier staged cancers compared to observed data. Secondly, testing

parameters will attempt to reflect technological changes and advancements that are likely to occur (Abbas, 2021). This can help determine if changes to modern technologies should be considered and whether introducing potentially more expensive technologies can be absorbed within the model.

Quality-Adjusted Life-Years

The benefits gained from this economic analysis are based on health utilities (QALYs) for different lung cancer stages. As the QALY application is relatively new in the health economics realm, there is limited data on different health state utilities (Whitehead & Ali, 2010). Denmark approved the use of QALYs only in January 2021, and their uptake in health economics is currently limited (Plesner, 2020). In line with the lack of data, most studies have not explored QALY states within their sensitivity analyses. This thesis will examine QALY sensitivities through confidence intervals provided by the cost-effectiveness study by Kowada (2022). These confidence interval ranges are displayed in Table 15, and were obtained from expert, patient and public respondents in the meta-analysis by Sturza (2010).

Post-Diagnosis Mortality

The mortality rate of the diagnosed population was adjusted in intervals of +/-20% from the base case, reflecting slight decreases in lung cancer mortality seen globally (IARC, 2021) and possible, but not expected, increases. Despite a slight decrease in mortality rates, Denmark currently has the third-highest mortality rate in Europe for lung cancer.

Discounting Rates

Adjustments for future costs and QALYs to their present value will be performed by challenging the discount rate assumptions. Denmark's discount rates for costs and QALYs are equally set at 4% (Finansministeriet, n.d.). The European Commission recommends varied discount rates based on a country's specific economic landscape, with 5% applied to EU member states with less advanced economies that will typically experience higher economic growth rates and 3% applied to other member states (Haacker et al., 2019). Currently, 85% of studies sampled in the Global Health Cost-Effectiveness Registry database apply a discount rate of 3% (Haacker et al., 2019). Some nations apply lower discount rates to benefits than costs, indicating an increase in health status over time after diagnosis and treatment (Haacker et al., 2019). This sensitivity analysis will explore cost discount rates from 3-5%, as seen in other literature and upon recommendation from the European Commission (Hofer et al., 2015; Snowsill et al., 2018; Haacker et al., 2019; de Koning et al., 2020; Du et al., 2020). The QALY discount rates will be varied from 1.5 to 4%, as reflected in other studies (Hofer et al., 2015; Snowsill et al., 2018; de Koning et al., 2020; Du et al., 2020)

Screening and Treatment Costs

Introducing a LCSP could lead to new priorities in budget allocations from the Danish Health Authorities. Future advancements in research and technology will impact and shift clinical practice away from current interventions (Drummond et al., 2015). This can lead to changes in costs of medical technologies and treatments over time caused by expiring patents, design efficiencies, and demand for services change (Drummond et al., 2015). It is discussed by the Danish Lung Cancer Group and Saghir (2021) that costs of lung cancer surgery have decreased dramatically over the past decade due to less invasive surgical procedures, while costs for chemotherapy have increased due to the developments in targeted therapies. The cost of the screening program and lung cancer treatment has been adjusted to compensate for these fluctuations, with upper and lower bound limits set at +/-50%. This threshold was used in the reference paper by Hofer et al. (2017) and can be seen in other economic analyses (Snowsill et al., 2018; Du et al., 2020).

4.5.1.2 Two- and Multi-Way Deterministic Sensitivity Analysis

The combined effects of all parameters cannot be interpreted using a one-way analysis and can therefore underestimate the uncertainty surrounding the decisions (Drummond et al., 2015). A multi-way sensitivity analysis can represent an analysis between two parameters and can be constructed using parameters set at extreme yet plausible scenarios. Difficulties in interpreting a multi-way sensitivity analysis can arise from the low probabilities of these scenarios eventuating within a model. Such events can be seen as unlikely, meaning sensitivity testing of extreme circumstances can be questioned as to whether or not it is genuinely uncertain.

It must be addressed that this thesis performed some of its DSA testing using an iterative method after the one-way DSA testing was performed. In doing so, the most sensitive parameters were identified and further explored against other parameter variations. Other two- and multi-way sensitivities within this EE were sourced from literature to reflect historical changes in healthcare or from other CUAs to strengthen their use. The two- and multi-way sensitivity analysis will be presented in a graph in the results section with the chosen baseline ICER. In contrast to the CEP, the costs will populate X-axis and the QALYs on the Y-axis, with the most acute-angled ICER presenting the most cost-effective solution.

The two-way DSA parameters chosen to explore were adherence, treatment costs, screening costs, LDCT sensitivity, and diagnosis sensitivity. Once adherence and treatment costs were identified in the single-way DSA testing as sensitive parameters, they were further scrutinized against multiple model input parameters. Outlined below are the chosen two- and multi-way DSA parameter combinations and the justification for their use.

Best and Worst Case

The literature shows that multi-way DSAs are conducted to determine the best and worst-case scenarios (Drummond et al., 2015). The parameters with the highest sensitivity were identified through single DSAs; adherence, treatment cost, and screening costs. These parameters will be combined in order to construct the outer thresholds. As seen in other economic analyses, all parameters varied by +/-50% (Peters et al., 2022).

Adherence, Screening Costs, and Treatment Costs

As adherence was identified as a highly sensitive parameter, it will be measured against both the treatment and screening costs to determine the extent of uncertainty. As with the worst and best-case scenarios, all parameters will be varied by +/-50% based on other CUAs (Peters et al., 2022). The goal is to ascertain where other model parameters could compensate for alterations in adherence.

Screening Sensitivity and Screening Costs

Innovations in healthcare have historically been associated with higher expenditure (Topol, 2015). This thesis will mimic these changes by altering the sensitivity of LDCT by screening by +/-20% and the screening costs by +/-50%. Doing so will determine if upgrading to newer and more advanced technologies can overcome the investment required by the Danish Ministry of Health. This multi-way sensitivity was not observed in other CUA studies. However, as this thesis focuses on healthcare in innovation, the researchers decided to determine if investments in innovation could be cost-effective within this LCSP.

There are several limitations to the DSA approach. (1) The parameter ranges are often decided upon arbitrarily, (2) it is not possible to observe non-linearities within the model, (3) correlations between parameters cannot be determined, and (4) the DSAs are usually reported as ICERS. This thesis has, when able to, used literature to support the formulation of parameter ranges. The non-linear relationships and correlations between parameters have been explored through varied multi-way sensitivity analyses. Inevitably, not all parameters will be able to be combined within the multi-way DSA, which could lead to questions surrounding model robustness. As the ICER itself presents limitations, the results will be presented and explored on a granular level and will attempt to determine the reasoning behind changes to the ICER.

Table 15. Sensitivity Upper and Lower Bounds Overview

Assumption	Current Value	Lower bound	Upper bound
Adherence	58%	29%	87%
Disease Progression Transition Probabilities			
No Lung Cancer	0.965	0.968	0.963
Stage I	0.370	0.608	0.132
Stage II	0.494	0.685	0.302
Stage IIIA	0.477	0.662	0.292
Stage IIIB	0.781	0.798	0.764
Stage IV	0.702	0.702	0.702
Diagnosis Sensitivity			
Standard Clinical Pathway	2-65%	50%	150%
LDCT	43-98%	80%	120%
QALYs			
No Lung Cancer	0.891	0.891	0.9
Stage I	0.825	0.7	0.9
Stage II	0.825	0.7	0.9
Stage IIIA	0.772	0.6	0.8
Stage IIIB	0.573	0.6	0.8
Stage IV	0.573	0.3	0.6
Post-Diagnosis Mortality Rate			
Post-diagnosis mortality	8-69%	80%	120%
Discount rates			
Cost Discounts	4%	3%	5%
QALY discounts	4%	1.50%	5%
Screening Costs			
LDCT Screening Costs	1,844	922	2,765
Treatment Cost			
Stage I	264,157	396,236	132,079
Stage II	258,585	387,877	129,292
Stage IIIA	397,829	596,744	198,915
Stage IIIB	506,462	759,693	253,231
Stage IV	706,717	1,060,075	353,358

Note. Sources in text

4.5.2 Probabilistic Sensitivity Analysis

PSAs have a growing role in determining parameter uncertainty due to the limitations of DSAs. The NICE in the UK recommends using a PSA to demonstrate the consequences of parameter uncertainty (Briggs, 2005). The use of a PSA can provide the opportunity to determine statistical-based statements surrounding the impacts of uncertainty on the cost-effectiveness of a model (Drummond et al., 2015). A PSA assigns distributions to each model parameter and given alpha and beta parameters, with random samples generating empirical distributions of costs and effects often through Monte Carlo simulations (Hatswell et al., 2018). The net benefits from the model can be calculated by each sample from the model generating a single estimate of expected costs and benefits, then repeating in large volumes (e.g., 10,000 times) (Drummond et al., 2015). The results of the costs and outcomes are stored and graphed to illustrate what the ICER could have been. The output graphed in the CEP can then be analyzed to determine the proportion of the results within the cost-effectiveness threshold (Hatswell et al., 2018). Furthermore, a cost-effectiveness acceptability curve (CEA) can represent the trajectory of the results (Hatswell et al., 2018).

As per Briggs et al. (2006), each parameter's distribution must be determined, described, and justified to perform a PSA. Beta distributions are generally applied for the probabilities as they have a binomial range from 0 to 1 (Drummond et al., 2015). The cost data typically assign gamma distributions as they cannot present negative results. QALY data is also commonly assigned gamma distributions as there is an upper bound of 1 with technically no lower bound. However, applying a PSA statistical approach is not without its limitations. The distribution choices can lead to further criticism within the model, such as the distributions determined through arbitrary means (A. Briggs, 2005). Briggs (2005) also comments that it is still possible to perform a PSA when parameters are informed by secondary information, such as literature. However, the subjective opinions of the researchers will often determine the parameter distributions.

This thesis could not perform PSA testing due to a lack of data availability on the alpha and beta parameters. Estimating these could risk parameter uncertainty or second-order uncertainty (Drummond et al., 2015). Without evidentiary support from the literature, estimating parameters would invalidate the requirements to explicitly justify the distribution and parameters, which would, in turn, question the credibility of the assumptions made (Drummond et al., 2015). The researchers did not wish to create additional sources of structural uncertainty within the model. The DSA method was, therefore, the chosen method for sensitivity testing.

In summary, this thesis will use both single, two- and multiway deterministic sensitivity analyses to test the robustness of the model. The assumptions within the model will be tested, with variations of the base values

adjusted to reflect the literature or changes to technologies or pathways. The results will be displayed and discussed extensively in the text by applying them to the Danish context.

5. Results

This section presents the results of the EE by illustrating the decision tree with probabilities, showing the starting cohort Markov model, the Markov model results and ICER calculation, and the sensitivity analysis.

5.1 Illustrated Decision Tree with Data

The decision tree in the appendix illustrates the pathways that patients can take when getting diagnosed with lung cancer. The two figures illustrate the LDCT screening group and the current pathway's possible paths. The available link can allow the reader a closer view of the decision tree, nodes, and branches: Decision tree.

5.2 Markov Model Results

This thesis conducted two Markov models with two purposes. The first simulation produced the starting cohort for the second Markov model. This section presents the output values for each cancer stage after simulating a Markov model for 30 cycles. The second part shows the second Markov model simulated for 15 cycles for both the screening and the comparator cohort. The output from the second Markov model is then used to calculate the ICER and cost-effectiveness.

5.2.1 Starting Distribution

Table 16 illustrates the distribution calculated using the probabilities and stages explained in the methodology section, simulating a Markov model for 30 cycles. The output percentages from the 30-cycle Markov model are then used as input distribution in the primary Markov model used to calculate the ICER. The percentage output was multiplied by the risk cohort of 106,041 to arrive at a starting distribution for no lung cancer and the different cancer stages.

Table 16. Calculating Input Values for the Markov Cohort-Simulation Model

	No lung cancer	Stage I	Stage II	Stage IIIA	Stage IIIB	Stage IV
Output	15,161	117	66	30	9	25
Percentage output	98,39%	0,76%	0,43%	0,20%	0,06%	0,16%
Input	104,338	802	457	210	62	172

Note. References in text

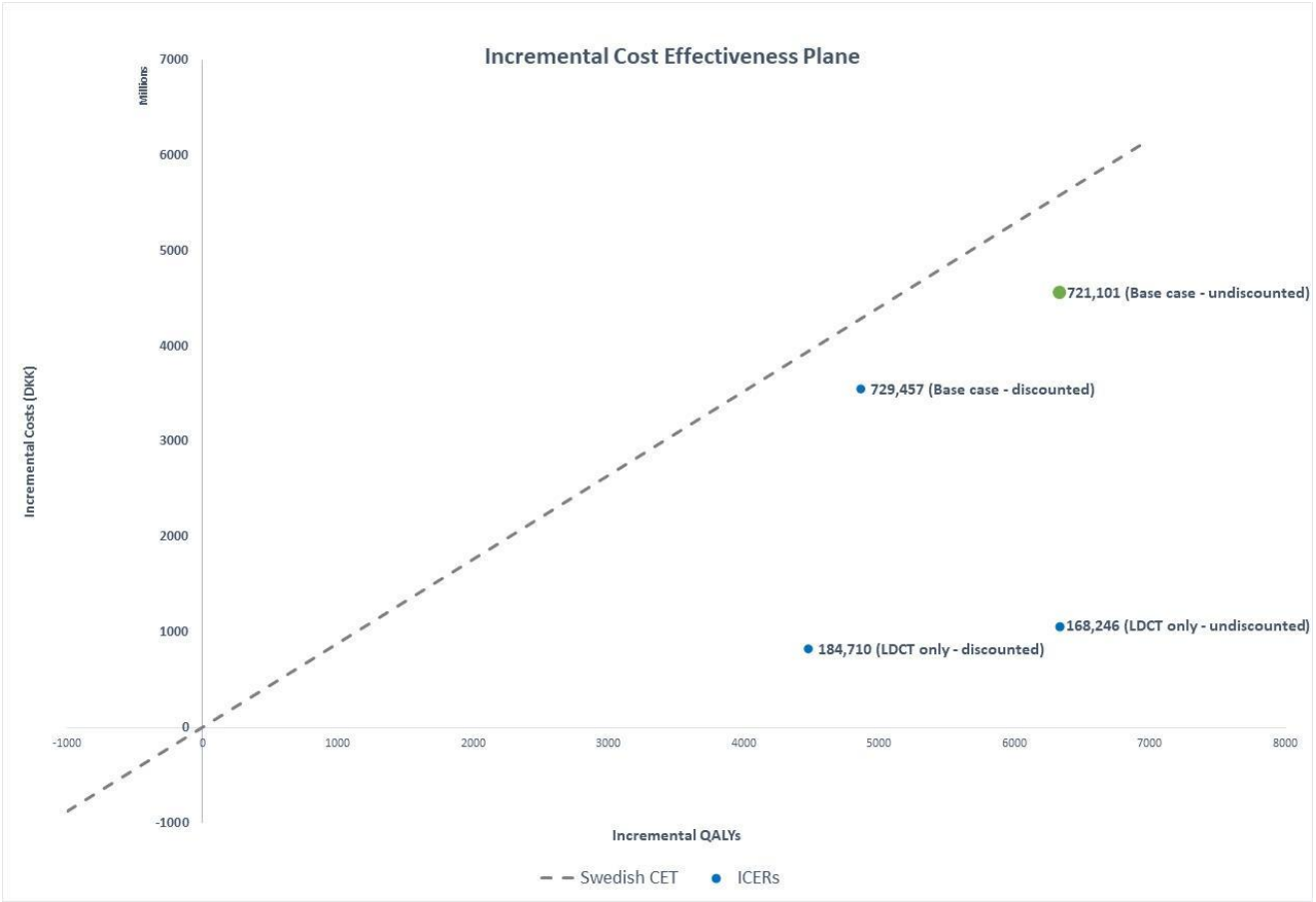
5.2.2 Incremental Cost-Effectiveness Ratio

The primary Markov model simulation resulted in total costs and QALYs used to calculate the ICER, with the starting distribution calculated based on the output from the first Markov model. The total incremental cost for 15 cycles is 4,565,071,950 DKK, and the respective total incremental QALYs for the 15 cycles are 6,331. This results in an ICER or cost per QALY of 721,101 and 0.06 QALYs gained per person in the screening cohort. As illustrated in Figure 8, the ICER falls in the northeast quadrant under the CET. Therefore, the LDCT screening is considered cost-effective, using the total non-discounted costs and QALYs after 15 years. The costs are higher, but the effects are also higher.

$$ICER = \frac{Total\ Cost\ LDCT - Total\ Cost\ Current}{Total\ Effect\ LDCT - Total\ Effect\ Current} = \frac{\Delta Costs}{\Delta QALYs}$$

$$721{,}101 = \frac{5{,}503{,}457{,}083 - 938{,}385{,}132}{905{,}944 - 899{,}614}$$

Figure 7. Markov Model Cost-Effectiveness Plane



Calculating the ICER by only including the cost of LDCT, excluding the treatment cost, results in an ICER of 168,246 DKK per QALY. This result is calculated by setting the cost for the current pathway to a zero versus the cost of LDCT scans.

$$168{,}246 = \frac{899\,614 - 0}{905{,}944 - 899{,}614}.$$

The cost and QALYs are not the only interesting output values from the Markov model. Table 17 below summarizes other interesting results that should be considered when evaluating the two options. The total lung cancer death decreased by 882 people (3517 - 2635) for the screening group compared to the current pathway after 15 cycle years. The complete diagnosed population is 2,153 more people in the screening group versus the non-screening group. Among these, 1,684 more people get detected in stage I and 667 more people in stage II for the screening group compared to the current pathway. 295 more people get detected in stage IV in the current pathway versus the screening group. In the screening group, 58% adhere, and the remaining 42% go through the existing pathway, which means that the screening group includes people getting detected through screening and current care. A detailed representation of the differences in diagnosis in the different stages can be found in the Appendix.

Table 17. Summary of Results

Event, 15 year Markov model	Current Diagnostic Pathway	LDCT Screening
Total Cost (undiscounted)	938,385,132	5,503,457,083
Total QALYs (undiscounted)	899,614	905,944
ICER (undiscounted) 721,101		
Total Cost (discounted)	742,356,416	4,022,510,810
Total QALYs (discounted)	698,494	702 971,86
ICER (discounted) 732,504		
Total lung cancer death	3,517	2,635
Total death	33,137	32,255
Total diagnosed	1,537	3,690
Total cost of screening program	0	1,065,116,825

5.2.2 Deterministic Sensitivity Analyses

The output from the DSA is illustrated in the Tornado diagram and two- and multi-way sensitivity graph (Figure 9 and 10). These graphs demonstrate how robust and sensitive the different tested parameters are. Twenty-seven single and multi-way sensitivity analyses have been performed as shown below. The more significant results will be analyzed and discussed further.

Table 18. Summary of Undiscounted Sensitivity Results

Sensitivity Results - Undiscounted							
	Current Pathway		Screening Program		Incremental Difference		Estimated ICER
Single-Way DSA	QALYs	Cost	QALYs	Cost	QALYS	Cost	ICER
Base case	899,614	938,385,132	905,944	5,503,457,083	6,331	4,565,071,950	721,101
Screening Program Only	899,614	-	905,944	1,065,116,825	6,331	1,065,116,825	168,246
LDCT sensitivity +20%	899,614	938,385,132	906,984	5,286,300,610	7,371	4,347,915,478	589,895
LDCT sensitivity -20%	899,614	938,385,132	904,823	5,581,141,779	5,209	4,642,756,646	891,280
Adherence -50%	899,614	938,385,132	902,965	5,142,561,487	3,352	4,204,176,355	1,254,396
Adherence +50%	899,614	938,385,132	908,414	5,801,688,596	8,800	4,863,303,464	552,619
Adherence -25%	899,614	938,385,132	904,528	5,333,626,595	4,915	4,395,241,462	894,276
Adherence +25%	899,614	938,385,132	907,234	5,658,003,213	7,620	4,719,618,080	619,361
QALYs best	910,028	938,385,132	916,854	5,503,457,083	6,827	4,565,071,950	668,718
QALYs worst	896,615	938,385,132	902,139	5,503,457,083	5,524	4,565,071,950	826,410
Discounting QALY 1.5% / Cost 4%	899,614	938,385,132	905,944	5,503,457,083	6,331	4,565,071,950	721,101
Discounting QALY 3% / Cost 3%	899,614	938,385,132	905,944	5,503,457,083	6,331	4,565,071,950	721,101
LDCT cost -50%	899,614	938,385,132	905,944	4,970,898,670	6,331	4,032,513,538	636,978
LDCT cost +50%	899,614	938,385,132	905,944	6,036,015,495	6,331	5,097,630,363	805,224
Lung cancer treatment costs +50%	899,614	1,299,502,815	905,944	7,211,458,514	6,331	5,911,955,699	933,856
Lung cancer treatment costs -50%	899,614	433,167,605	905,944	3,113,897,388	6,331	2,680,729,783	423,449
Diagnosis through current pathway +50%	900,235	1,164,421,828	906,156	5,556,858,942	5,921	4,392,437,114	741,842
Diagnosis through current pathway -50%	898,962	590,662,752	905,729	5,439,739,723	6,766	4,849,076,971	716,664
Lung cancer mortality rate +20%	899,353	938,385,132	904,815	5,503,457,083	5,462	4,565,071,950	835,779
Lung cancer mortality rate -20%	899,967	938,385,132	907,308	5,503,457,083	7,340	4,565,071,950	621,921
Lung Cancer Disease Progression +50%	889,034	1,586,467,263	897,530	6,163,504,004	8,496	4,577,036,741	538,758
Lung Cancer Disease Progression -50%	910,186	420,424,195	914,172	4,927,439,189	3,986	4,507,014,994	1,130,611
Multi-Way DSA							
Adherence -50% and LDCT screening cost -50%	899,614	938,385,132	902,965	4,876,073,555	3,352	3,937,688,423	1,174,884
Adherence +50% and LDCT screening cost -50%	899,614	938,385,132	908,414	5,003,325,598	8,800	4,064,940,465	461,901
Best case (adherence +50%, all costs -50%)	899,614	433,167,605	908,414	2,739,414,189	8,800	2,306,246,584	262,060
Worst case (adherence -50%, all costs +50%)	899,614	1,299,502,815	902,965	7,182,951,010	3,352	5,883,448,195	1,755,439
Adherence +50% with treatment costs -50%	899,614	433,167,605	908,414	3,537,777,187	8,800	3,104,609,582	352,778
Adherence -50% with treatment costs -50%	899,614	433,167,605	902,965	2,660,804,935	3,352	2,227,637,330	664,658
Screening costs +50%, LDCT sensitivity +20%	899,614	938,385,132	906,984	5,819,155,563	7,371	4,880,770,431	662,189

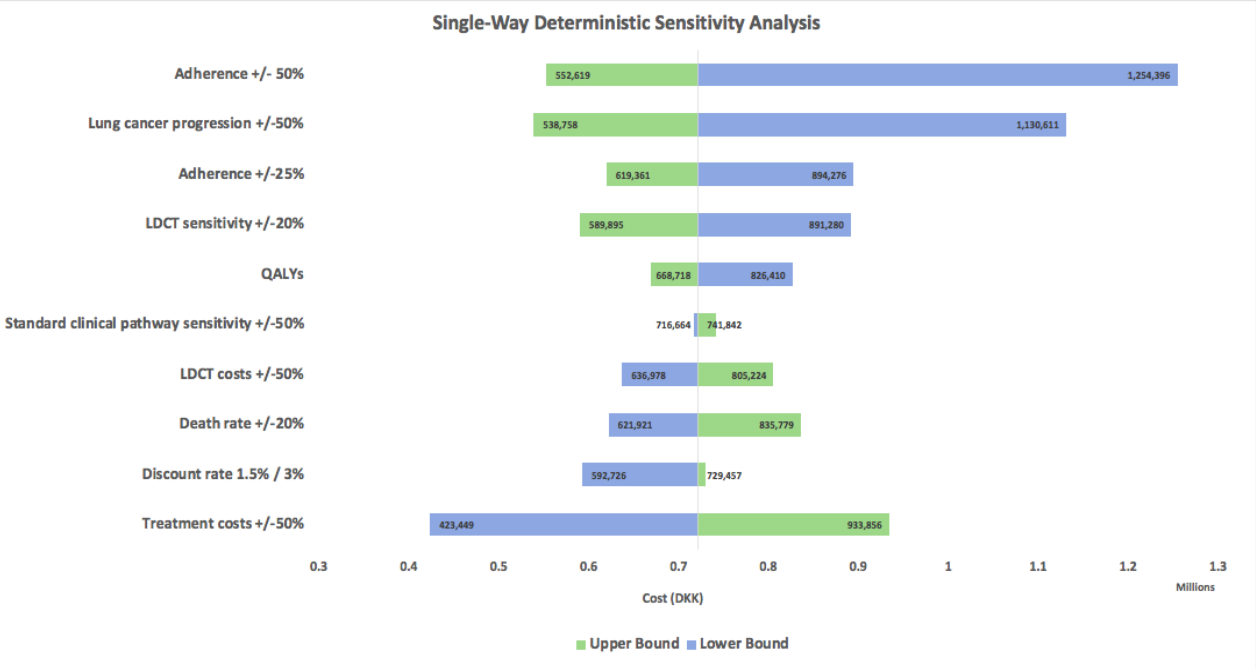
Table 18 shows that the uncertain parameters are decreased LDCT sensitivity by 20%, decreased adherence from 25% onwards, increased treatment cost by 50%, and decreased lung cancer progression by 50%. These parameters are uncertain because the change of parameters results in an ICER above the CET, making the screening program no longer cost-effective.

Table 19. Summary of Discounted Sensitivity Results

Sensitivity Results - Discounted							
	Current Pathway		Screening Program		Incremental Difference		Estimated ICER
Single-Way DSA	**QALYs**	**Cost**	**QALYs**	**Cost**	**QALYS**	**Cost**	**ICER**
Base case	698,494	742,356,416	702,972	4,022,510,810	4,478	3,280,154,394	**732,470**
Screening Program Only	698,494	-	702,972	827,172,205	4,478	827,172,205	**184,710**
LDCT sensitivity +20%	698,494	742,356,416	703,706	3,889,331,480	5,212	3,146,975,064	**603,737**
LDCT sensitivity -20%	698,494	742,356,416	702,180	4,056,216,846	3,686	3,313,860,430	**898,944**
Adherence -50%	698,494	742,356,416	700,870	3,674,436,629	2,377	2,932,080,213	**1,233,772**
Adherence +50%	698,494	742,356,416	704,717	4,317,097,360	6,224	3,574,740,944	**574,362**
Adherence -25%	741,605	784,513,327	745,384	4,166,362,488	3,779	3,381,849,161	**894,975**
Adherence +25%	741,605	784,513,327	747,460	4,486,653,366	5,855	3,702,140,039	**632,309**
QALYs best	706,575	742,356,416	711,401	4,022,510,810	4,826	3,280,154,394	**679,658**
QALYs worst	696,171	742,356,416	700,081	4,022,510,810	3,911	3,280,154,394	**838,796**
Discounting QALY 1.5% / Cost 4%	814,668	742,356,416	820,202	4,022,510,810	5,534	3,280,154,394	**592,726**
Discounting QALY 3% / Cost 3%	741,605	784,513,327	746,470	4,333,309,754	4,865	3,548,796,426	**729,457**
LDCT cost -50%	741,605	784,513,327	746,470	3,894,219,147	4,865	3,109,705,819	**639,202**
LDCT cost +50%	741,605	784,513,327	746,470	4,772,400,360	4,865	3,987,887,033	**819,713**
LC treatment cost +50%	741,605	1,086,416,698	746,470	5,662,942,938	4,865	4,576,526,240	**940,708**
LC treatment costs -50%	741,605	362,138,899	746,470	2,473,101,789	4,865	2,110,962,889	**433,910**
Dx through current pathway +50%	742,082	978,621,508	746,635	4,381,074,374	4,553	3,402,452,865	**747,226**
Dx through current pathway -50%	741,103	490,194,967	746,302	4,276,668,630	5,199	3,786,473,663	**728,257**
LC Death rate +20%	741,402	784,513,327	745,623	4,333,309,754	4,221	3,548,796,426	**840,793**
LC death rate -20%	741,880	784,513,327	747,490	4,333,309,754	5,610	3,548,796,426	**632,563**
LC Progression +50%	691,338	1,234,915,330	697,322	4,533,061,248	5,984	3,298,145,919	**551,151**
LC Progression -50%	705,644	347,164,953	708,504	3,575,315,409	2,860	3,228,150,456	**1,128,747**
Multi-Way DSA							
Adherence -50% and LDCT screening cost -50%	741,605	784,513,327	744,186	3,761,327,881	2,580	2,976,814,554	**1,153,676**
Adherence +50% and LDCT screening cost -50%	741,605	784,513,327	748,367	3,971,732,474	6,762	3,187,219,147	**471,368**
Best case (adherence +50%, all costs -50%)	741,605	362,138,899	748,367	2,187,785,383	6,762	1,825,646,483	**270,001**
Worst case (adherence -50%, all costs +50%)	741,605	1,086,416,698	744,186	5,563,670,446	2,580	4,477,253,748	**1,735,176**
Adherence +50% with treatment costs -50%	741,605	362,138,899	748,367	2,846,035,372	6,762	2,483,896,473	**367,351**
Adherence -50% with treatment costs -50%	741,605	362,138,899	744,186	2,074,270,398	2,580	1,712,131,498	**663,543**
Screening costs +50%, LDCT sensitivity +20%	741,605	784,513,327	747,269	4,622,255,414	5,663	3,837,742,087	**677,685**

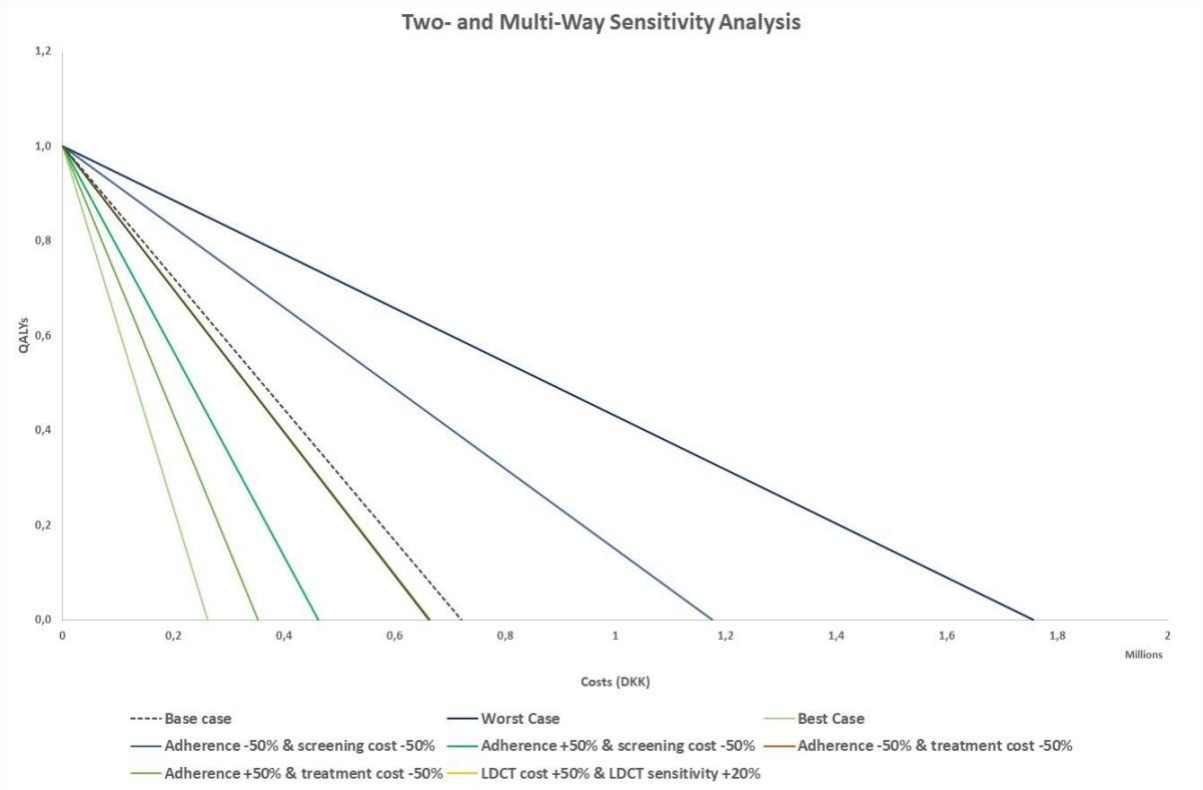
Table 19 shows that the uncertain parameters are the same as for the discounted cost and QALY values. The ICER has changes as a result of the applied discount rate of 4% for both costs and QALYs.

Figure 8. Tornado Diagram of One-Way Deterministic Sensitivity Analysis



The above tornado diagram displays the output simultaneously from the sensitivities when varied. The green bars represent the upper bound, where the input parameters were increased, and the blue shows the lower bound, where the parameters were decreased. The midline is set at the base case ICER at 721,101 DKK/QALY. The larger bars display higher variance from the midline as seen with adherence, lung cancer progression, and treatment costs. The smaller bars show minimal change, as seen with the standard clinical pathway.

Figure 9. Two- and Multi-Way Sensitivity Analysis



Lastly, figure 10 illustrates the two- and multi-way sensitivity analysis performed. The x-axis is the cost (DKK), and the y-axis is QALYs. The dotted line is the base case ICER, with variations in the ICERs falling to their respective sides. The best and worst-case scenarios combining adherence, treatment, and screening costs are shown as the outer bounds. There is overlap with the LDCT costs of +50%, LDCT sensitivity +20%, adherence -50%, and treatment cost -50%.

In conclusion, the results have produced an ICER which is costly. However, there are significant epidemiological benefits gained from LCSP regarding reduced morbidity and mortality. Some high variation was seen in the sensitivity analysis, including adherence and costs, highlighting areas of weakness in the model. The most significant results will be discussed further regarding the numerical changes and the subsequent impact towards the Danish and innovation context.

6. Discussion

This section discusses the results in light of the research question; *Why should the Danish Ministry of Health consider a lung cancer screening program for detecting lung cancer among a heavy-smoking population aged 55-74 years?* It considers the results from the EE, sensitivity analysis, and broader views outside of the scope of this EE that also has to be taken into account when considering new healthcare interventions in the Danish healthcare system.

6.1 Epidemiological Results and Incremental Cost-Effectiveness Ratio

The first part of the discussion relates the results to the methodological choices, logical reasoning, and analysis. The ICER result in this thesis is not the only interesting result to consider when considering if Denmark should implement a LCSP. The epidemiological results reveal the impact of introducing a LCSP in the Danish setting, as more patients get diagnosed in earlier stages, and fewer individuals die. Therefore, the first part of this section will discuss the epidemiological results, and the second part will present the ICER results.

Epidemiological Effects

By introducing a LCSP in Denmark, the number of people diagnosed would initially increase the incidence of lung cancer. Screening would result in 419 additional lung cancers discovered in the first year alone, or a 2-fold increase from the standard clinical pathway. This increase is due to the higher detection rates when using LDCT screening for all-stage lung cancer, as opposed to more patients developing lung cancer. Furthermore, the all-stage diagnosis rate from a LCSP increases to 2.4-fold when observed from a 15-year perspective. Within this increase, the diagnosis through a LCSP accounts for 75% of all diagnoses in the intervention group.

These results display highly positive effects when observing morbidity at a granular level. Focusing on the first year of diagnosis, there is an 11-fold increase in stage I lung cancers discovered. The increased detection is due to screening via LDCT being 17-times more effective in detecting Stage I lung cancer than the standard clinical pathway. This diagnostic trend continues further in the model, and after 15 cycles, there are almost 10-fold detection of lung cancers in stage I in the LDCT group than in the standard clinical care group. When observing the overall prevalence of late-stage lung cancer, there is a decrease within the screening group. There are 47% fewer stage IIIB and 29% fewer stage IV lung cancers detected instead of the standard clinical pathway. More people have already been diagnosed in the earlier stages rather than progressed to later stages through the normal disease progression and pathways.

These positive findings are similarly reflected in the total estimated mortality. After 15-years, the LCSP group displayed 882 fewer deaths from lung cancer than the standard clinical pathway. The decrease subsequently

means there is an all-stage 25% reduction in mortality rate from lung cancer compared to the screening group, a mortality decrease similar to that produced by the NLST and NELSON clinical trials (Snowsill et al., 2018). This reduction in lung cancer mortality is linked to the probability of dying in the different diagnosis stages, as patients will live longer if diagnosed at an earlier stage of lung cancer. As already stated, Veronesi et al. (2013) explained that surgical resection is only possible in 20% of symptomatic lung cancer cases. With lung cancer being detected in earlier stages through screening, the overall mortality from lung cancer is expected to decline. When observing the lung cancer mortality in relation to all-cause mortality, there is a 2.7% reduction in the overall death rate. By reducing lung cancer mortality significantly, it reduces the mortality in the overall high-risk population. These are similar results as seen from Hofer et al. (2018). The screening program might help lower cancer mortality in Denmark, being the third highest in Europe.

The model reported a surplus of 0.06 QALYs gained per person within the screening cohort, due to patients having a higher survival rate when diagnosed earlier. Table 1 (Lung cancer treatment by stage) shows a 60-70% five-year survival rate in stage I compared to a 10-15% five-year survival rate in stage IV. The mortality results from the Markov model have aligned with the literature that survivability depends on lung cancer diagnosis stages since fewer people die if they get diagnosed early (Popper, 2016). This intrinsically means that patients who are detected early would have the opportunity to get treatment at an earlier stage, stop or slow the disease progression and live for longer, resulting in higher survivability.

Denmark should establish the importance and weight of epidemiological benefits gained from introducing a LCSP. Diagnosing lung cancer at earlier stages will provide more curative treatment options and increase life expectancy, something that the Danish government should prioritize. It could be argued that the benefits would outweigh the costs associated with the program, with the positive effects felt by patients, families, and also society. The following section will discuss the weighting of cost to outcomes using the ICER results.

Incremental Cost-Effectiveness Ratios

The total undiscounted cost per QALY is 721,101 DKK, including the cost for treatment and LDCT scanning for 15-cycles in the Markov model. This result is cost-effective, and the intervention should be adopted in Denmark, given that the CET is 881,316 DKK/QALY since the cost of producing better health outcomes is acceptable. In comparison, the ICER, when only including the cost for the LCSP, is 168,246 DKK/QALY. This ICER is lower since the costs for treatment are not included. Since the overall number of patients being diagnosed through the LDCT screening is improved, the cost for treatment will be higher for this cohort even though more patients are diagnosed in earlier stages with lower treatment costs. The QALYs stay the same in both ICERs, being higher for the LDCT screening group since more people are diagnosed early before

progressing into the higher stages with lower QALY values. Also, there are fewer deaths associated with a QALY value of zero.

The ICER, including treatment cost, is the main ICER as it shows the total cost effect of introducing the new intervention. Laupacis (2002) argues that the effect and not costs determine if one should adopt a new intervention or not. At the same time, the issue of scarce resources in healthcare budgets is vital, and the cost factor is essential to consider, which is why the more inclusive result was chosen as the main ICER.

The results section also presents the discounted ICER of 732,504 DKK/QALYs, slightly higher when calculating future costs and QALYs. When investigating the incremental costs and QALYs, both are lower figures reflective of a 4% discounted rate. The higher ICER results from the marginally more significant negative incremental change for the QALYs. This discount rate has subsequently provided less QALYs overall than costs; hence a slightly higher ICER is produced. Due to scrutiny applied to discounting rates, the sensitivity results from the adjusted discounting rates will be discussed further. One could argue that the discounted ICER should have been used as the main ICER due to individual social time preferences taken into consideration in the discounted ICER. However, Danish decision-makers should be aware that uncertainty about the future and the associated discounted rates applied can bring some skepticism toward discounted ICERs (Cleemput et al., 2008). For this reason, the base case ICER has been chosen as our benchmark to compare other results.

One can also discuss the different ICERs by comparing the different cycle outcomes. Table 3 and 4 in the appendix shows the different ICERs for one-year cycle times of five, 10, 15, 20, and 30-cycle years. The lowest ICER out of these is the 15 cycles. The first cycles are higher and aligned with previous research saying that screening gets more effective after a few years (Peters et al., 2022). There are patients in all stages of the natural history part of the model in the first years, and the effect of early-stage diagnosis is not evident. After a few cycles, fewer people are in the later stages, and more are diagnosed only in the early stages, which results in higher QALYs and lower ICER. The QALY values are relatively increasing with every cycle, i.e., the gap between QALY values increases between the alternatives for every increase in cycle years in favor of the LDCT screening.

After 15 cycles, the ICER goes up again even though the QALYs are increasing. One explanation for this could be that the costs are overestimated in the post-diagnosis model. The only way patients leave the model is when they die. Otherwise, patients stay in the post-diagnosis model and get treated every cycle associated with treatment costs. Even though the same thing happens with the standard pathway cohort, more people in this simulation are diagnosed in the later stages and die faster. This leads to a lower cost for this group due to how

the model is structured. So even though fewer people get screened, and more people are diagnosed in the lower, less expensive treatment stages with time, the costs increase. The 15-cycle ICER was chosen as the main ICER since most CUAs have chosen this time horizon and not because it was associated with a favorable result. The researchers did not know this would result before deciding on the time horizon.

Having discussed the different ICER outputs does not give us much valuable information since the ICER value does not hold much value on its own. The number has to be put into perspective and in relation to something else, especially given that Denmark has no threshold. Therefore, the following discussion sections will first discuss the sensitivity of the results. Then the ICER will be related to a discussion about the threshold it is compared against and compared to other ICERs from similar CUA studies.

6.2 Sensitivity Analysis Results

Sensitivity analysis was conducted to test uncertainties in the parameters to evaluate the robustness of the results. The single-, two-and multi-way deterministic sensitivity analyses examine the variations in the input parameters (Drummond et al., 2015). The results from the sensitivity analysis showed that the model was most sensitive to a decrease in adherence, which was present in both single-, two- and multi-way testing. However, many of the other parameter variations demonstrated high levels of robustness within the model, as discussed below.

Low robustness was seen within the model when adjusting the adherence rates. As the leading cause of instability, adherence was tested with multiple scenarios to determine where the most significant impact was seen and where other parameters could absorb the adverse effects within the model. Lowering adherence by 25% caused the model to no longer be cost-effective, with an ICER increase of 24% to 894,276 DKK/QALY. Furthermore, when adherence was reduced by 50%, the ICER inflated by 74% to 1,254,369 DKK/QALY. When screening adherence decreases, there is a reduction in QALYs from the screening group as fewer people are diagnosed in the early stages. Lowering adherence allows the disease to progress to later stages with lower associated QALY values, and the lowered QALYs outweigh the costs saved from not screening populations. Seen consistently across both single and multi-way sensitivities, adherence is a crucial factor that will need to be considered by the Danish government prior to introducing a potential LCSP.

The effects were not as positively dramatic when increasing the adherence rate. When adherence was increased by 25% and 50%, the ICER decreased by 14% and 23%. The decline could be due to the higher QALY output in the screening group. Even though the costs go up due to increased overall treatment and more people getting

screened, the cost does not increase significantly. An explanation could be that the early-stage treatment is less expensive than the later stages.

Two-way and multi-way sensitivities were conducted to determine if other model elements could absorb the adherence uncertainty. When testing against decreasing screening costs, the model could not withstand decreased adherence rates. The only scenario that could buffer a decrease in adherence was reducing the treatment costs by 50%, producing an ICER of 664,658 DKK/QALY, 8% lower than the base case. The QALYs in this scenario are lower since fewer people are diagnosed in the early stages. However, the lowered costs affect the screening group more, as more people in this group are diagnosed than through the current pathway. This optimistic scenario would require lung cancer treatment to innovate cost-effectively, either through more efficient technologies or by introducing generic treatment options offered as the primary treatment (Miller, 2020).

Careful attention needs to be paid before implementing a LCSP, as increasing costs can expose the payer to an economically ineffective program. The program costs were explored through several single and multi-way DSAs. Plausible worst and best-case scenarios were created, with the best-case scenario being where adherence increased by 50% and all costs decreased by 50%, showing an ICER reduction of 64%. This ICER reduction resulted from higher screening uptake, leading to higher cancer detection in earlier stages and thereby higher QALY rates, with subsequent treatment able to proceed at lower costs. Alternately, the worst-case scenario outcome presented for the inverse scenario produced an ICER that inflated to 143% over the base case outcome to 1,755,439 DKK/QALY. The increase was due to the lowered total QALYs for the screening cohort, due to adherence that kept people being screened through the current pathway. Furthermore, higher costs affect the non-adhering screening cohort more because more people are diagnosed in this group, leading to an overall higher cost increase than the current cohort.

The model showed less robust results when lowering treatment costs. Adjusting lung cancer treatment costs by -50% decreased the ICER by 41% to 423,449 DKK/QALY due to cost reductions in the screening group and the current clinical pathway. However, this scenario may not be realistic as lung cancer treatment costs have increased in the last decade (Danish Lung Cancer Group & Saghir, 2021). With oncological therapy becoming more specialized and targeted, the primary treatment for stage III-IV lung cancer has led to higher costs (Danish Lung Cancer Group & Saghir, 2021). However, costs have decreased in the past decade for early-stage lung cancers with less-invasive VATS surgical procedures as the primary treatment (Danish Lung Cancer Group & Saghir, 2021). With oncology being the primary treatment in late-stage cancers, reducing the prevalence of stage III-IV lung cancers through early detection will reduce lung cancer costs overall. The sensitivity analysis also tested increasing the treatment costs by 50%, which only produced a 30% increase of

the ICER to 933,856 DKK/QALY or about 50,000 DKK over the Swedish CET. Despite the ICER no longer being cost-effective, the model can withstand significant treatment cost increases, and the ICER does not dramatically exceed the CET.

Further analyses were conducted to determine if improving the current clinical pathway for diagnosis would improve the ICER. The sensitivities of the standard clinical diagnostic pathway were adjusted, which produced robust and unaffected results, with an ICER still below the Swedish CET. When the sensitivity of current diagnostic pathways was adjusted by +/-50%, the ICER changed by -1% and 3%, respectively. As the diagnosis rates are meager currently, there is minimal impact on the QALYs in the current pathway when improving and streamlining standard diagnosis. Therefore, it is not recommended to focus on enhancing current diagnostic pathways as the impact on reducing lung cancer costs is so minimal. Instead, it is recommended to look to innovations that can contain costs and enhance diagnosis capabilities.

Additionally, the sensitivity of LDCT screening was increased by 20%, leading to higher accuracy in diagnosis. The subsequent ICER fell by 18% to 589,895 DKK/QALY. This theory of upgrading to advanced technologies was explored further by introducing a cost element, combining the increase in LDCT screening sensitivity with a 50% increase in costs. The ICER remained robust and was reduced by 8% to 662,189 DKK/QALY. This sensitivity outcome demonstrates that investing in innovative and highly sensitive technologies, despite the increasing costs, would be economically beneficial to a lung cancer screening program and other users of the technologies, which should be a factor considered by Denmark when establishing a LCSP.

Looking into the changes within lung cancer as a disease, the progression and mortality rates post-diagnosis were explored through single-way DSAs. Mortality rates for post-diagnosis lung cancer have been slowly decreasing over the past decade (Jakobsen et al., 2013), and sensitivity testing was used to estimate this effect in the future. The mortality rate for the diagnosed population was adjusted to +/-20%, with an ICER of 621,921 DKK/QALY established for the lower bound. This outcome results from the QALYs within the screening cohort increasing more than the current pathway cohort since more patients are getting diagnosed than in the current cohort. These results should be of interest to Denmark, as decreasing mortality from lung cancer will inherently decrease costs for such programs.

From observing lung cancer progression, the upper and lower bounds were adjusted to +/-50%, respectively. This change decreased the ICER to 538,758 DKK/QALY when cancer progressed faster versus 1,130,611 DKK/QALY when lung cancer progressed slower. Fewer cancers are detected in the current clinical pathway with decreased progression as they are not progressing to late stages, where they are more likely to be detected. This would lead to higher overall QALYs in this cohort due to low detection rates and lower treatment costs.

Low-stage cancers have a high detection rate in a screening program, and these cancers are treated at the detection stage in higher volumes, leading to increased costs. The incremental difference between the costs and effects of the two groups resulted in lower QALYs with higher costs, creating a poor ICER.

The increased progression rate led to a better ICER since the QALYs for the screening group went up, and QALYs for the standard pathway group went down. More patients progress to late-stage cancer and die faster in the current cohort. The screening cohort diagnoses more people in the early stages before they progress to the later stages, and the cost has gone up in the screening group due to treatment requirements. The cost for the current pathway also went up, which can be due to more people progressing to the more expensive stages faster, associated with a higher cost. Lung cancer disease progression is only included in the pre-diagnostic stage within our model. Changes in these probabilities would represent pathophysiological changes within lung cancer itself. Therefore, as this is a very hypothetical situation, it was not included in the multi-way sensitivity. Not explored in our study is the post-diagnosis disease progression, which would give the Danish decision-makers insight into how initiating treatment could affect costs and QALYs.

Denmark does not currently have QALY weights established for lung cancer. It will need to develop these within a local context if they wish to implement cost per QALY within its economic evaluations. Considering the methods for collecting QALYs in a Danish context should be considered as this can bias results (Drummond et al., 2015). This thesis determined health benefits by obtaining QALY data through the standard gamble methods. This method uses uncertainty and generally produces higher scores than other collection methods. To measure the impact alternate QALY collection methods may have had on the ICER, QALY sensitivities were also explored in single-way DSAs. The upper and lower bound confidence intervals from Kowada (2022) were applied to the QALYs, producing an ICER that increased by 15% and decreased by 7%, respectively. Both ICERs remained below the CET, displaying robustness against QALY changes. These variations indicate a potential underestimation of QALY weights due to the use of the standard gamble collection method can be compensated for by this model.

The sensitivity analyzes around discount rates were extended to reflect those used in other European countries. Denmark's current discount rate for costs and benefits is set at 4%, and the sensitivities have challenged these inputs. Many neighboring countries to Denmark have different discount rates, with discount rates applied to reflect a country's current economic standpoint (Kellerborg et al., 2020). When the differential discount perspective was applied, as in the Netherlands, with a cost discount rate of 4% and a benefit rate of 1.5% (Versteegh et al., 2016), an ICER of 592,726 DKK/QALY was produced. The QALYs in both the screening and current clinical pathway group were almost fixed throughout the EE life cycle, as the lower discounting

meant they held their weight throughout the later cycles. This indicates a higher total QALY for the same cost when applying the 1.5% rate.

Interestingly, there was almost no change from the base case discount ICER when a discount rate of 3% was applied to the costs, which is the discount rate set in Germany, Ireland, and Sweden. Drummond et al. (2015) discussed that there will always be cost constraints regarding healthcare expenditure, which supports maintaining discount rates for both costs and benefits at the same level. Changing Denmark's discount rates for EEs is unlikely to occur unless more substantial evidence is produced to support changes. With a Dutch differential discounting policy applied to our EE, a LCSP would seem more attractive to the intended audience. Observing other countries and how discounting policies impact their health and economic choices could benefit both the Danish government and the populations receiving care.

To summarize the sensitivity analysis, all the parameters showed robustness to the model except for decreased adherence from 25% onwards, increased treatment cost by 50%, decreased lung cancer progression of 50%, or decreased LDCT sensitivity by 20%. Investing in newer technologies instead of improving standard diagnostic processes has improved the ICER, with robustness seen in most other parameters. However, in multi-way sensitivity testing, favorable circumstances only presented with cost decreases. The ICER was higher than the threshold for changes in these parameters due to lowered effects or higher costs. Since the CET determines if the intervention is cost-effective or not and plays a vital role in the analysis, the next section will discuss the threshold.

6.3 Cost-Effectiveness Threshold

Denmark does not have a CET. Instead, this thesis uses the implicit Swedish threshold converted to 881,316 DKK/QALY to determine if the LDCT screening intervention is cost-effective compared to the standard pathway. Since the LDCT is more expensive but more effective, the threshold is essential in determining if the ICER in the northeast quadrant is cost-effective. There are several approaches to determining the threshold, and it can therefore be challenging to know which CET to use for this thesis. Therefore, the use of the threshold has to be communicated to the decision-maker.

The preferred approach in this thesis would have been the precedent method or the opportunity cost method to arrive at a Danish CET. For the precedent method, one could collect data on the cost-effectiveness of other cancer screening programs implemented in Denmark since there is no current screening program comparator for lung cancer in Denmark. Denmark offers free national screening programs for breast cancer, cervical cancer, and bowel and rectal cancer (Danish Health Authority, 2021). The researchers did not do this because

there is no cost-effectiveness data available for these programs either. Furthermore, this kind of comparison would not be wholly accurate since the screening technologies are meant to detect different cancers. Even though this is a suitable method, it is difficult to use in real situations due to variations between diseases.

The second opportunity cost method suggests separate budgets for different types of interventions. If a CET for other cancer screening programs were available, or if the decision-maker could compare the cost and health outcomes for these programs to the results in this thesis, this would be good guidance in deciding on the budget allocation. This data is not available but might become more available, making it possible to evaluate league tables with alternative therapeutic strategies to develop a suitable CET.

The motivation behind using the upper bound of the implicit Swedish threshold can be discussed. On the one hand, lung cancer is most normal amongst people from lower socioeconomic backgrounds and due to self-inflicted behavior, which might lead to lower prioritization (Tetzlaff et al., 2021). On the other hand, cancer is generally given a more significant portion of the healthcare budget historically and in comparison to other diseases (Trasta, 2018), which supports the assumption to use an upper bound of the Swedish threshold for this EE. The rule-of-thumb threshold in Sweden is 356,240 DKK (500,000 SEK) (Svensson et al., 2015) and if this CET would have been applied, the ICER would not have been cost-effective.

The ICER would not be cost-effective if adopting the other thresholds, identified in the *Cost-Effectiveness Threshold* section, from Ireland, Poland, America, or Canada. Although, according to the upper bound of the international definition, the base case ICER produced from this EE would be below the international threshold. Furthermore, the Danish government has adopted the NICE guidelines to some extent, and therefore the UK threshold might be a suitable option. For extending life treatments in end-of-life care, the UK threshold is 447,869 DKK/QALY, which means the intervention is not cost-effective since the ICER would be above this threshold and too expensive. To conclude, the use of CET determines if the new interventions are cost-effective or not since they are usually more costly but also more effective. This thesis would benefit from having more clear guidance regarding a CET since the ICER is not not cost-effective when adopting the upper range of threshold values, or when using other countries' implicit or explicit thresholds.

6.4 Cost-Utility Analysis Literature

Discussing this EE's findings with that of other literature can assist Denmark in contextualizing the conclusions presented. The validity and reliability of this thesis and ICER can be discussed through comparison with other CUAs and guide decision-makers even further. As explained in the literature review, the most relevant CUAs on LDCT screening produce varied ICERs due to the different methodological choices made for each EE. The

literature did not explain many detailed methodological choices and raw data due to cohort-simulation models or poor literature transparency. This section will first discuss the ICER results, the model choices, cost perspectives, and the epidemiological results.

Several of the epidemiological outcomes were reflected in this thesis' model from the literature. The model estimated a 21% reduction in mortality, similar to that of the NELSON, MILD, LUSI, and NLST RCTs (Field et al., 2016; Becker et al., 2019; Pastorino et al., 2019; de Koning et al., 2020), with the results, were also mirrored in CUAs (Hofer et al., 2018; Criss et al., 2019; Toumazis et al., 2019). This reduction in mortality was also seen in overall QALYs gained in this thesis' output, with 0.06 QALYs gained per person in the screening cohort, the same as Hofer et al. (2018) and Field et al. (2016). The similarities observed between this thesis and the literature indicate strong external validity. The strong correlations further endorse the recommendations of introducing a LCSP, and that Denmark should prioritize both saving and improving the lives of its citizens.

When comparing the results to that of other CUAs, this model's ICER is higher than all others except the EE performed in the US setting, which could be a consequence of variations between treatment and screening costs. However, it can also be due to wide-ranging methodological choices within each EE. Almost every CUA examined within this thesis has methodological choices that vary. Multiple studies compare single screening sessions to annual and biennial screening starting with the screening intervention. High-risk inclusion criteria have been determined using risk prediction tools, with participants aged 50-80 years. Sources from starting and transition probabilities vary from both RCTs and literature, with QALY data obtained from various literature sources. Modeling approaches also vary within each study, from Markov models to newer, less validated methods, such as lung cancer outcome simulators. Cost data has been sourced from governments, insurance companies, and registries. Discount rates for costs and QALYs have been applied at rates reflective of the country in which the CUA has been conducted. Due to these inconsistencies stemming from the methodological choices, uniformly comparing the ICER results should be performed with caution. For Denmark to compare their results to others, CUA guidelines should be developed nationally or adopted from other countries, such as the NICE guidelines used within the UK. Doing so will assist decision-makers in determining the viability of CUAs through the use of equal comparators, as the EE would employ similar methodological choices.

Studying the model choices more closely, there have only been three CUAs performed on a LCSP using a Markov Model in the past decade (Peters et al., 2022). Therefore, directly comparing the results to other studies is complex as the model choice will affect the outcome. Although this thesis models many decisions from the methodological choices of Hofer et al. (2018), comparing the results in both the base case and sensitivities is

logical here. Hofer et al. (2018) produced an ICER of € 30,291/QALY, or 225,353 DKK/QALY. The differences noted are the treatment costs of lung cancer and screening costs, which were between 30-75% lower than the cost within Denmark. The ICER can also differ due to this thesis' model's simplified nature, as disease progression post-diagnosis, aftercare, and the associated mortality rate was not included. Since the model in this thesis does not have those stages, only the probability of surviving in the same stage of diagnosis, this could lead to an overestimation of treatment costs. With higher diagnosis rates in the early stages and low mortality rates, many patients will continue to receive treatment within the model longer than in reality. This inherently means a patient will stay in the same lung cancer stage, receiving the same treatment until they die. Since there was no data on aftercare or palliative care costs in Denmark, the model did not include these stages, which otherwise would have been preferred.

Consistency in the literature was seen across a choice of the payer as a cost perspective, with no study yet to choose the societal perspective within their cost methods. This aspect reinforced the researcher's choice of payer perspective methods for this thesis. However, the payer perspective does not encompass the actual costs placed upon society and how this might impact the ICER. Although no CUAs currently exist using the societal perspective, producing results using the societal perspective would be challenging to validate. With the model already being sensitive to cost variations, there is a risk that introducing a societal perspective would produce an ICER above the CET, making the program economically unviable. Providing cost from a payer perspective risks underestimating the true ICER, which can be misleading to decision-makers.

In conclusion, the ICER produced from this thesis is higher than all non-U.S. CUAs produced. Apart from the epidemiological gains seen across studies, limited methodological similarities are found across the literature on CUAs for introducing a LCSP. Comparing results across studies should be done with vigilance, as methodological choices taken by researchers will indicate variance in the results. Therefore, the ICER in this study could not be validated compared to other CUAs because the differences in methodological choices made it infeasible. No single economic metric used in isolation, such as cost per QALY, should be used as the basis for decision-makers (Gafni & Birch, 2006). Hence the contextual application of the results needs also to occur. Therefore, the next section will discuss the applicability of the LCSP in the Danish context.

6.5 Danish Context

There are also other factors than the ICER and epidemiological results that affect whether Denmark should implement a LDCT screening program or not. These are factors outside of this EE that, for example, can be social, structural, political, and healthcare professional-related issues that could make an implementation unfeasible.

Social Barriers to Adherence

The social barriers to implementing the screening program would first be connected to adherence to sensitivity analysis. There are several uncertainties associated with adherence. Moldovanu et al. (2021) say that a barrier to low adherence is the inability to consistently and systematically identify the people in the risk group. Therefore, the first concerning question is: (1) How do you reach out to the risk group? There is no smoking register in Denmark, so a survey has to be sent out to the age group in question to gather information on the habits of those people and then identify the persons eligible for a screening program.

The second question of concern would be: (2) What is the likelihood that people will answer the survey or contact the organization responsible for the screening program? The highest incidence of lung cancer is amongst people from lower SES, with Moldovanu et al. (2021) saying that people with extensive smoking history from the lower SES are less likely to attend LCSP. On the other hand, other studies, such as the one from Sakoda et al. (2021), say that people in age 65-71 years who have previously smoked but are not current smokers are more likely to adhere. Therefore, it is difficult to predict how many people would fill out the form or contact the organization responsible for the screening.

Furthermore, (3) Once the risk group is contacted, would they adhere to the screening program? Accessibility could be an issue since people in lower SES might face geographical issues related to traveling time and cost. Therefore, it is difficult to know if and how many people in the risk group will adhere to the screening program, even though they are identified and contacted. The only way to find out is to do a pilot study or investigate the behavior amongst these people in Denmark, according to the expert opinion of Dr. Saghir (2022).

(4) Could there be skepticism against the screening program? Patients might not want to be screened because of the harms connected to the scanning, including radiation exposure and the risk of reaction to contrast materials when used (Allen et al., 2019). Furthermore, people might not want to attend a screening program since the false positive rate is still high, as seen by 33% false positive rates in the NLST trial's first and second screening rounds. The technology might not be developed enough for people to trust the diagnostic method. People eligible for screening can also experience negative psychological elements, such as fear of being judged and pessimism about survival chances for the early stages of cancer, leading to lower adherence (Quaife et al., 2018).

In conclusion, there is a lot of uncertainty related to predicting the adherence rate for the screening program. Since the most sensitive parameter in this study is adherence, the issue has to be further explored before recommending Denmark implement a LDCT screening for lung cancer.

Structural Barriers

This EE shows that increasing the diagnosis in current pathways by 50% does not affect the outcome. Therefore, the decision-makers should not make the current pathway for diagnosis more effective but instead, look into other innovations such as LDCT screening. However, this could lead to structural barriers to the healthcare system. First, it would require 20-40 additional radiologists to interpret the scans, according to Bigaard (2022). Secondly, it would lead to a higher resource burden on the actual treatment process since more people are diagnosed and increase cancer spending, which would affect the budget and thereby politically related discussions.

The first structural barrier could be related to the hospitals. If educated radiologists are available, the health care professionals would potentially benefit from introducing the LCSP through LDCT scans. From this, less pressure would be placed on the GPs to interpret the patient's symptoms and risk factors. The signs and symptoms can be hard to recognize, and the early stages of lung cancer are usually asymptomatic and, consequently, often undetected. Therefore, it can be difficult and stressful for the GPs to detect cancer, and a national LCSP could help ease the stress on the clinicians. Although research also shows that eligible patients are more likely to undergo screening when their GP endorses attendance, the GPs should still be a part of the diagnosis process (Moldovanu et al., 2022). This could be dealt with by the screening organization identifying patients at higher risk and the GP informing patients, subsequently endorsing a LDCT. It would help to solve the issue of clinicians' unfamiliarity with eligibility criteria and the balance between harms and benefits for different risk groups when identifying people eligible for screening.

The LDCT will lead to a higher diagnosis rate in the early stages and, therefore, also a higher overall treatment burden. The increased capacity burden for hospitals has to be investigated on a national level so that hospitals do not experience bottlenecks in the treatment process after patients have been diagnosed. As earlier explained, The Cancer Patient Pathways prescribed standards for maximum waiting of 42 calendar days from lung cancer diagnostics to treatment. If the capacity for more patients is not in place, this would not lead to an improvement of the system but instead lead to new problems after the diagnosis stage. It is unethical to provide a diagnosis but not offer treatment, and if bottlenecks are present, it will lead to a glut of diagnosed but untreated patients.

Implementing a LDCT LCSP would also lead to changes in the healthcare budget allocation. More radiologists would have to be employed and potentially more lung cancer treatment personnel, affecting the budget and other parts of the health system already in place. Although, at the same time, more patients will be diagnosed in stage I than stage IV after a few years of a LCSP. Since the cost of treating patients in Denmark is higher in the later stages, according to Green (2015), the prices might fall even though the cost of screening is added to the budget.

Table 1 in the appendix shows the treatment cost for the different stages after simulating the Markov model for 15 cycles. Here, one can see that the total cost for stage IIIB and IV is higher for the current pathway (156,055,303 + 644,360,591) than for the screening cohort (83,209,014 + 457,197,784). Although, at the same time the costs for the earlier stages are higher for the screening cohort (454,923,764 + 201,625,838 + 166,186,767 for screening versus 45,751,607 + 29,829,622 + 62,387,907 for current) since more people are diagnosed in these stages, even though the actual treatment for these are lower. Note that the limitations of the post-diagnosis model, discussed in the limitation section, will explain why these costs are potentially overestimated and the treatment costs might be lower, especially for the early stages. Interestingly, however, there are 842 people diagnosed in stage IV for the current pathway, and the cost for these is 644,360,591 DKK, while there are 1,590 patients diagnosed in the screening group, with the total cost for these being 454,923,764 DKK. More people are getting diagnosed for a lower cost in stage I for the screening group than there are for the lower number of patients diagnosed in the current pathway for stage IV with a higher cost. Changing the adherence to 100% will decrease the total treatment cost of stage IV by 278,870,197 DKK (644,360,591 DKK-365,490,394 DKK) for the screening group. To conclude, the higher the adherence to the screening program, the lower the cost for later stages will be since more people will be diagnosed in the earlier, less expensive stages.

There might also be political barriers to implementing a LDCT LCSP regarding screening program approval and the subsequent budgeting allocations. The main factors used in decreasing lung cancer mortality are early detection and smoking cessation (Schabath & Cote, 2019). Some critics argue that one should go to the root cause of the problem and stop people from smoking, to work with *preventive care* instead of *sick care*. Denmark has unveiled plans saying no citizens born after 2010 are allowed to buy cigarettes or nicotine products (Euronews, 2022). However, this kind of argument and policy does not help the patients who have smoked for 30 pack-years already. When discussing the lung cancer screening submission made by Dr. Saghir and the Danish Lung Cancer Screening Society (2022), there is bipartisan support for the program across the political parties. Using both methods will help to lower lung cancer incidence since smoking is the main factor for developing lung cancer. The question is how these two should be combined and targeted towards the eligible risk group.

To conclude the discussion, the primary consideration Denmark has to evaluate are CETs in EEs, adherence, cost, and investments in screening technologies, when deciding if the intervention should be considered or not. Overall, there do not seem to be solid structural barriers in the Danish healthcare system to introducing a LCSP. However, a clear plan regarding resources, implementation, and education have to be established for the program to be successful within the Danish context.

7. Limitations

When creating the economic model used in this thesis, several assumptions had to be made. To account for sensitivity in the model, parameters were tested as discussed in the previous section though single and multi-way DSAs. Even though parameters were tested and Drummond et al. 's (2015) six requirements for conducting an EE were fulfilled, there is still uncertainty in the Markov model and in this thesis as a whole. This section will list the main limitations to the model that has not already been mentioned in the methodology section. Limitations to the thesis as a whole and its generalizability will also be discussed.

7.1 Markov model

According to Sculpher et al. (2006) decision-analytic methodology is the framework capable of meeting all requirements for the decision-makers. However, the quality of the model is dependent on the evidence it is built on and the structural assumptions have to reflect a real world scenario (Drummond et al., 2015). In order to identify the limitations to the model in a structured manner, the checklist for assessing quality in decision-analytic models developed by Philips et al. (2004) will be used as a guidance. This checklist is structured in three main parts being (1) structure, (2) data, and (3) consistency. The following sections will discuss the limitations to the Markov model, guided by the checklist from Philips et al. (2004) and end by discussing the sensitivities, internal and external validity.

Structure

The objective and perspectives used in the EE is clearly stated and the intervention pathways are aligned with evidence. Even though the structural assumptions are explained and reasonable for the analysis, some of them have to be mentioned as limitations. Firstly, a time-dependent Markov model could have been beneficial since age is a factor affecting the likelihood of treatment success, outcome prognosis, and mortality. A higher age should be given a higher probability of dying of both lung cancer and all-causes. Since no people enter the model, one could say that the mortality rates should have been increased in the later cycles, compared to the early ones, since one knows the cohort is aging for every cycle.

Secondly, the memoryless assumption could be seen as a bad representation of the real life progression of lung cancer and underestimate the progression rate of the disease. One could argue that the longer a patient has been in a stage, the faster the progression prognosis should be. Since the progression rate parameter is making the model sensitive in the DSA, this could affect the cost-effectiveness of the ICER result.

Thirdly there are no individuals entering the model over the 15 cycles, but only patients leaving the model through the absorbing death stage. Since the defined risk group is within a specific age group and smoke-pack

year history, it would make sense that individuals could enter the model or leave the model by not being in the eligible risk group anymore. The model instead simulates the 15 cycles with the same cohort, as a simplified version of a real life context.

Fourth, the duration element of the post-diagnosis stages also adds to the list of structural limitations. In the post-diagnosis model, there is only the death transition and no disease progression, aftercare, or palliative care stage. The duration a person stays in stage I is therefore probably overestimated, given that the patients will stay in that stage until they die. The probability of dying in stage IV for the post-diagnosis model is 69% and therefore the later stages do not face the same duration problem as they die quicker. Furthermore, patients in stage IV cannot progress to a later stage in real life but for the early stage's disease progression this is possible. This also means that the stage IV is more realistic, even though it does not include the aftercare or palliative care stages either.

Data

Some of the choices made in the Markov model were due to data availability. First and foremost, the only identified study with the defined lung cancer stages I-IV with stated transition probabilities for the disease progression before diagnosis were identified in Hofer et al.'s (2018) study. The transition probabilities were created by Hofer et al. (2015) through a Bayesian calibration method and German incidence data were used and taken from the German Center for Cancer Registry Data. Since Germans do not differ too much from the Danish population, the use of German epidemiology data was considered acceptable. However, it would have been preferred to derive data from epidemiological or observational studies from Denmark, to calculate the Markov states progression. Although, a limitation to the Markov states would still remain since the whole identification of transition probabilities between Markov states can be questioned. How can one predict how disease progresses between stages of undiagnosed patients? The only way to study this is to determine disease progression from diagnosed but untreated cohorts, otherwise this will continue to be a limitation in the future research since the data on undetected incidence will not be available in the future either. To account for this uncertainty, the researchers tested the probabilities in the DSA and the analysis of the outcome as stated in the discussion. Since the parameters were sensitive, this limitation remains and poses uncertainty to the model and results.

When the diagnosis probabilities were modeled the probability of getting diagnosed in the current pathway and the non-adherence group for the screening cohort were the same. The assumption is that all the diagnosed in the non-adherence screening group (equalling 42% going through the current pathway) were removed before the diagnosed through screening "had a chance" to get diagnosed. The amount of people getting diagnosed through the current pathway might therefore be overestimated and the amount of diagnosed through screening

cohort underestimated. Furthermore, there might be differences between the German and Danish detection process of diagnosis. The diagnosis probabilities were taken from the German study and therefore follows the probability of getting diagnosed through this healthcare system more so than the Danish pathway.

In regards to the mortality probabilities, these should have been time dependent, and the risk of dying should have increased in the later cycles in comparison to the early stages. Furthermore, the probability of dying in the undiagnosed stage is lower than for those in the diagnosed stage, except for in stage I where it is the opposite. It might not be reasonable to say that there is a 130% increase (from 29.78% to 69%) in death between undiagnosed and diagnosed stage IV patients. As discussed by Snowsill et al. (2018), mortality rates in pre-clinical lung cancer are uncertain, yet it is widely believed that death as a result of lung cancer occurs post-diagnosis. A paradox presents in that a diagnosis should not necessarily accelerate death, however a lack of diagnosis may constitute mild symptoms which do not directly lead to death.

The process after diagnosis was brought together to one treatment stage for each cancer stage. The death probability for the post diagnosis model is therefore the same, even though the probabilities between treatment and death, aftercare and death, and palliative care and death are not the same (Hofer et al., 2018). Here, the death probability of one year was applied and stayed the same in the sequent cycles. A two year death probability after diagnosis should have been applied for the following cycle, and so on. This leads to an underestimation of the mortality rates in the post-diagnosis part of the model.

The QALY values remain stable throughout the whole model, independent of how long an individual has been in a certain stage. While in reality, patients might change the perception of severity of one stage after being in that stage for a long time. The QALY estimation might therefore not be representative of that state over a longer time period. Although, since the survivability forecast is low for patients with lung cancer, this might not be a large limitation since the probability of dying is quite high. A further limitation for utility measures is that QALYs remain the same in the same stages throughout the 15 cycles, meaning no other events that could affect the QALY value are taken into account in the model. Since the risk group are heavy smokers in an older age range, the probability of other diseases or lowered life quality is likely in reality (Rojewski et al., 2016). A third limitation related to QALYs is that some CUA studies report that radiation can affect people who have been screened for many cycles who might be physically affected by this. These patients should therefore have a lower QALY than people who haven't been screened for less cycles and therefore have not been exposed to as much radiation.

The costs of determining a true-positive diagnosis has also not been included in this Markov model, leading to an underestimation of diagnostic costs. To diagnose and stage lung cancer, further imaging and testing must

be performed, including but not limited to scans and biopsies. The cost data for the true-positives was not able to be averaged for the Danish context, as this is probably because it is difficult to estimate these figures. There is a large variation between diagnostic needs and costs, as a patient with obvious and extensive disease may not require the same detailed examination as a patient with stage I.

The cost for screening can also be underestimated since the false positive rates could pose extra costs in terms of resources used in diagnosis and psychological stress for the patient and the patient's family. On the other hand, the screening cost for the cohort might be lower since the probability that individuals would get screened for an executive 15 years is low. Furthermore, due to poor data availability, the preferred societal costs perspective was not able to be reliably estimated and included in the model. As previously explained, the costs would probably be higher if the societal perspective would be used. As the model is sensitive to large cost increases, applying the preferred cost perspective might make the results not cost-effective with an ICER above the threshold. Providing cost from a payer perspective risks providing an underestimation of the true ICER, which can be misleading to decision-makers.

More limitations connected to the cost data is that there was no Danish cost data on the aftercare or palliative care which affected the structure of the post diagnosis model. If this data would have been available, the structure of the model could have been improved and be a better representation of reality. This would solve the issue of the potentially overestimated costs for the lower stage cancers in the post-diagnosis model. Depending on the cost of aftercare and palliative care, the cost results might not have looked that different if they are the same as treatment costs, but one could assume they are lower in the earlier staged cancer as curative treatment is able to be offered.

The number of individuals in cohorts can also be discussed from different perspectives. Section 2.1.2 outlined the different risk factors for developing lung cancer, with the cohorts in this study only referring to two of these risk factors, being age and smoking history. One could therefore argue that more people should be included in the cohort. However, these people can also be difficult to identify and were therefore not included. Moreover, in reality there would be additional exclusion criteria which would deem a participant ineligible to be included in the program. This includes patients who have cancer, are above a certain weight, on home oxygen, recent weight loss or acute respiratory infection (Pedersen et al., 2017). This consequently can lead to an overestimation of the inclusion cohort, and the limitation is that one does not know the number of individuals that could be eligible for a screening program, in Denmark.

The adherence rate can also be questioned for being overestimated. The adherence rate stays the same for the 15 cycles but the likelihood that individuals would attend screening for an executive 15 years is low.

Furthermore, there are not enough studies to validate that a 58% adherence rate would be correct for those implementing the screening program. Although, this is the best estimation in a Danish context for 2022, according to studies (Kirkegaard, 2015) and experts within the field (Bigaard, 2022).

Consistency

The external consistency is about the fact that all relevant data available should be taken into account and incorporated in the model. Even though there is evidence of false positive results from LDCT screening from both RCTs and CUAs, this model does not account for false positives. The choice to exclude these numbers was made to simplify the model and also because no cost data for the false positives could be identified in the Danish context. Since all other costs were taken from Denmark, the researchers excluded the false positives and left its inclusion to future research. The model could therefore be overestimating the outcomes from the screening group, which should have a higher cost and a negative QALY value related to a false positive diagnosis. It is important to take this into consideration when concluding the ICER results.

External and Internal Validity

The model created for this thesis is based on a mix of different data sources. The costs are taken from the Danish context and will differ from costs in other countries. However, the interventions compared, risk group identified, probabilities of progression, and utility values could be used for studies in other countries similar to Denmark, such as Germany, the Netherlands, or Sweden. These countries are mentioned because parameters used in this model come from epidemiology data and economic models from these countries. The external validity in this study could therefore be argued to be high. Although, since costs have a great impact on the model output, these should be applied by the context being studied. The internal validity can be argued to be high since the researchers are transparent in choices of perspectives and data sources, conduct sensitivity analyses, and state all inclusion criteria and limitations to assumptions and excluded factors.

7.2 Sensitivity Analysis

A total of 27 single and multi-way sensitivity analysis tests were conducted to determine the uncertainties in the model. One could argue that DSA testing is too simplistic, and that inadequate multi-way sensitivity testing occurred with only 7 scenarios tested. Testing scenarios which are deemed to be implausible would produce results which simply present additional noise, distorting the base case ICER. Additional combinations of input assumptions would ultimately lead to flaws within the model, yet in the absence of additional time, the multi-way scenarios were kept to realistic ones. The parameters of the sensitivities were obtained from the literature, whilst some were estimated best-guesses, including the changes in disease progression, diagnostic and screening accuracy and associated costs. The lack of evidence to support these variations can deem the results to be inaccurate, however not testing these assumptions would lead to more significant limitations.

The absence of a PSA presents a large limitation in this study. It was not able to be performed as the alpha and beta parameters were unable to to be estimated accurately from the literature due to limited data availability. Undertaking PSA testing would enable the researchers to test at various parameters the probability of the intervention being cost-effective (A. H. Briggs & Gray, 1999). From here, a more accurate estimate of uncertainty within the model can be determined which would lie between the ranges produced in the DSA results. Without this testing, the comprehensiveness of the sensitivities can be questioned, however including a PSA would risk second-order uncertainty, or parameter uncertainty (A. Briggs et al., 2012). Furthermore, the results of the DSA would not be able to be compared against the PSA. Comparing the cost and QALY outcomes from the DSA and PSA would determine if there was agreement between the sensitivity analysis, further providing evidence of robustness within the model.

7.3 Non-Model Related Limitations

There are also other factors to this thesis that can add to the list of limitations. These could be the comparison to other screening programs in Denmark, identification and further analysis of the Danish context in terms of political, structural, social perspectives, expert insights, and patient views and behaviors. These are all limitations that would help the EE from being "just" an EE, bringing a more nuanced analysis of the landscape and essentially the feasibility of the screening program.

8. Conclusion

Several factors have to be considered when determining why the Danish Ministry of Health should consider a LCSP for detecting lung cancer amongst heavy smokers aged 55 to 74. The objective of this thesis was to primarily conduct an EE to answer the research question as the European Union recommends HTAs for assessing healthcare interventions' cost-effectiveness. Other factors such as previous research, epidemiological results, and the feasibility of the Danish context are also discussed.

The first reason why the Danish Health Authorities should consider a LCSP for heavy smokers in age 55 to 74 years old is that the chosen risk group has a higher probability of developing lung cancer than non-smokers at younger ages. Furthermore, research has shown that detection in earlier lung cancer stages increase survivability at the same time as Guldbrandt et al. (2015) state that the nature of lung cancer diagnosis in Denmark leads to diagnosis in later stages. New interventions should be evaluated and potentially introduced to improve early-stage diagnosis, looking at the current detection difficulties for early-stage lung cancer. However, knowing this is not enough to recommend the Danish Health Authorities consider a LCSP.

Healthcare decision-makers have to allocate a constrained budget between an overwhelming volume of new healthcare innovations and interventions. To guide decision-makers, HTAs and EEs can be conducted to assess the cost and the health outcome to arrive at the most cost-effective interventions to which resources should be allocated. Since this EE fulfilled all the requirements for decision-analytic modeling, a CUA was conducted, and a Markov model developed. This thesis contributes to the literature through the choice of evaluation since there is no CUA conducted on a LCSP in the Danish context.

The recommended screening innovation had to be identified first to evaluate if a LCSP should be implemented instead of or in parallel with the current clinical diagnosis pathway. Previous research has identified LDCT scanning as the preferred screening option for detecting lung cancer in 2022, so this intervention was compared to the current clinical pathway.

The results from this EE arrived in an undiscounted base case ICER of 721,101 DKK/QALY, being cost-effective given the upper bound of the Swedish CET of 881,316 DKK/QALY. The increased health outcomes are worth the higher costs of the intervention. This result would argue for why the Danish Ministry of Health should consider introducing a screening program. However, this ICER result comes with uncertainties, as shown when testing several parameters through a DSA.

The most sensitive parameter is adherence. However, the model result is sensitive to treatment costs, lung cancer progression, and LDCT screening sensitivity. It is important to mention that false positives are not included in the analysis, nor the post-diagnosis disease progression, which could affect the output. The uncertainties around the choice of CET also affect the interpretation of the ICER, which might not have been cost-effective using a lower CET. Therefore, it is difficult to conclude if the ICER result is robust or low enough to recommend the Danish Ministry of Health consider a LCSP despite the cost-effective result.

The researchers also compared the base-case ICER result to other CUA results on LDCT screening with the same comparator. The ICER in this study is higher than in other CUAs, due to higher healthcare costs within the Danish healthcare system. However, since the methodological approaches within the literature varied greatly, the comparison did not validate the cost-effectiveness result.

The epidemiological results showed that the screening program is preferred over the current clinical pathway for the chosen risk group. More patients are diagnosed in the early stages in the screening group, decreasing lung cancer mortality by 21%. This result would argue for a screening program in Denmark since the survivability is higher amongst the adherent screening patients getting detected at earlier stages.

When discussing the feasibility of a potential LCSP in Denmark, social behaviors, resource use, structural healthcare changes, and political agendas should be considered. Since this thesis has not researched these topics, it is difficult to conclude if a LCSP would be feasible in the Danish context. Although, after talking to experts on lung cancer, cancer screening programs, epidemiologists, and lung cancer physicians in Denmark, no significant barriers were identified to introducing the program.

The researchers believe that the Danish Ministry of Health should consider a LCSP based on the cost-effective results. However, based on the ICER alone, there are multiple uncertainties in the analysis. Difficulties arose in confirming the robustness of the base case ICER through sensitivity analysis and when comparing it to the existing literature. The model results also show that more patients are being diagnosed earlier, fewer individuals die, and no significant challenges in the Danish healthcare system are identified. Therefore, there are arguments for why the Danish Ministry of Health should consider an LCSP for detecting lung cancer among the risk group evaluated. Recommendations for further research are outlined below, which could give a more comprehensive evaluation of the feasibility of a LCSP in Denmark.

9. Future Perspectives

Following the five objectives in EEs, the last objective is to identify future research (Drummond et al., 2015). This can be done by exploring areas of uncertainty in the model structure and input parameters and identifying areas for further consideration. This section will elaborate on the uncertainties and suggest areas of valuable future research beyond the model.

As adherence was the most sensitive parameter affecting the ICER, research should be conducted to understand the psychosocial elements of adherence to cancer screening programs. There are multiple barriers to lung cancer screening adherence among patients identified in the literature. These include the stigma associated with lung cancer, reduced health literacy, lack of disease awareness, language barriers, fear of results, and access to services (Coughlin et al., 2020). Furthermore, barriers within the medical community should be addressed and further investigated. Failures currently exist both within the primary and acute healthcare settings, where eligible participants currently have low referral rates from physicians due to competing demands, lack of symptom awareness, low levels of shared decision-making, and evolving attitudes about the effectiveness of screening and lung cancer treatment (Carter-Harris & Gould, 2017). Addressing these barriers has been suggested to involve creating dedicated teams, expedited screening results for patients, utilization of mobile scanners to improve access to health care, and targeting the information needs of both medical and participating individuals. Addressing the root cause of barriers to adherence should be of a high priority to

establish and maintain the cost-effectiveness of a LCSP, as advanced infrastructure must be in place for the program to be successful.

The structural implementation barriers of introducing a LCSP have not been addressed in detail in this thesis but must be carefully planned and considered. When introducing a screening program, it is essential that resources are not diverted from other cost-effective healthcare interventions but instead used to enhance healthcare in harmony. When implementing the intervention, innovative methods should address the resource consumption around equipment, personnel, and information technology systems (Carter-Harris & Gould, 2017).

As previously mentioned in the discussion, investing in technologies with higher detection sensitivity has shown to be cost-effective, while advancements to the standard clinical pathway showed minimal effects. To compensate for this, utilizing innovation methodologies, such as the validated innovation model created by the Center for Integration of Medicine and Innovative Technologies, can further focus upon and facilitate the cycle of innovation (Brenan, 2011). Having robust methodologies to follow can provide structured guidance for healthcare decision-makers, enabling innovation and change. As the LDCT has a high false positive rate and the European Agency Health Technology Assessment has identified molecular biomarkers as an area for future research (EUnetHTA, 2020), other technologies should be considered. Biomarkers are said to have enormous potential but still require validation for widespread application.

Smoking is the leading risk factor for developing lung cancer, and it can be argued that preventative measures should be utilized further. Denmark is moving forward in these areas and has proposed new legislation to reduce the sale and consumption of cigarettes. However, smoking prevention programs should be considered in conjunction with a LCSP, as changing the behaviors of smokers will ultimately affect lung cancer rates. This area has to be further researched as some screening programs, including smoking cessation as a mandatory part, have led to lower attendance amongst smokers. For the risk group identified within this thesis, ceasing or reducing smoking may not offset the damage caused by extensive smoking history. However, it could bring benefits to future generations.

Denmark could also begin measuring health utilities for widespread use in economic analyses. As QALYs are relatively new health measurements, a fundamental approach should be utilized to begin collecting validated QALYs for different health states. Using health utilities from other countries risks misrepresenting results and having QALYs obtained in a localized context will provide greater accuracy in future EE research. Additionally, having QALYs specific to Denmark can allow for equity weights to be applied, which can help decision-makers in trade-off situations when allocating resources (Cookson et al., 2017).

Denmark does not yet have a CET established for EEs despite EEs being part of HTA and becoming a more popular method for assessing healthcare technologies globally. Given that the European council and parliament are adopting a new framework for HTA, which will be in place by 2025, one can assume that HTA reports will become increasingly used in Europe and Denmark. Without a threshold, it is impossible to determine if an intervention is cost-effective if the ICER falls in the northeast or southwest quadrant. Given that, typically, new interventions are more effective but more costly, a threshold is therefore needed to assess the health innovations. With multiple methods available for creating a CET, Denmark could focus research on establishing an appropriate CET within the Danish context. There are, however, risks and downsides of introducing a CET, including possible higher prices for interventions and decreased coverage. This leads to whether EEs should be a significant part of HTAs as the analysis is incomplete without a CET. One should also further investigate if the downsides of introducing a CET outweigh the positives. If so, other methods guiding the decision-makers could be explored, for instance, the ones stated in the introduction (Kristensen & Sigmund, 2008) or the relative net benefit (O'Mahony, 2015).

This thesis closes by giving the reader food for thought on the methods for EEs and the future of assessing healthcare innovations. The EU is adopting a framework for HTA to deal with current inefficiencies, intending to facilitate the joint clinical assessment of health technologies across the Union (European Commission, 2022). An EE's methodological choices and perspectives significantly affect the outcome. Therefore, the EU should provide structure for collaboration and the methodological frameworks and perspectives which should be followed. Data availability should also be considered when setting up the guidelines. This, to validate research against other literature and generalized to other member countries. The uncertainties between the different methodological choices and the use of CETs can limit the practical use of EEs, which the European Commission should focus on solving when moving towards introducing new *valuable* healthcare innovations.

10. Reference List

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11. Appendix

Appendix 1. Lung Cancer Screening Randomized Control Trials

Lung Cancer Screening Randomized Control Trials

Trial and country	Author, Year	Control	Intervention (CT schedule) 1 2 3 4 5 6 7 8 9 10	Participants	Age in years	Tobacco use in pack-years (PY)	Other risk factors	Outcome	False-positive rate (n =)
NLST	National Lung Screening Trial Research Team (2011)	Chest x-ray	■ ■ ■	53,454	55-74	>30 PY	If former smoker, quit <15 ago	15-20% mortality reduction	17,497
UKLS	Field et al. (2016)	No screening	■	4,055	50-70		Lung cancer risk >4.5% within 5 year	35% reduction, trial halted in pilot phase	494
NELSON	De Koning et al. (2020)	No screening	■ ■ ■	15,422	50-75	20 PY	If former smoker, quit <10 years ago	Mortality reduction 24% men and 33% females	343
DLCST	Wille et al. (2016)	No screening	■ ■ ■ ■ ■	4,104	50-70	20 PY	If former smoker, quit <10 years ago	No reduction in mortality	302
DANTE	Infante et al. (209)	Baseline chest x-ray then obervation	■ ■ ■ ■ ■	2,450	60-74	20 PY	Males only	Significant mortality reduction but limited statistical power	289
ITALUNG	Paci et al. (2017)	No screening	■ ■ ■ ■	3,206	50-74	30 PY	If former smoker, quit <10 years ago	16% mortality reduction	1006
MILD	Pastorino et al. (2019)	No screening	■ ■ ■ ■ ■ ■ ■ ■ ■ ■	4,099	>49 years	20 PY	If former smoker, quit <10 years ago	20% mortality reduction	88
LUSI	Becker et al. (2020)	No screening	■ ■ ■ ■ ■	4,052	50-69 years	30 PY	If former smoker, quit <10 years ago	26% mortality reduction	747
PanCan	Tammemagi et al., (2017)	No screening	■ ■ ■ ■	7,044	50-75 years	Ever-smokers	2% 6-year risk of lung cancer	Effective in detecting early stage lung cancer	N/A

Note. References in table

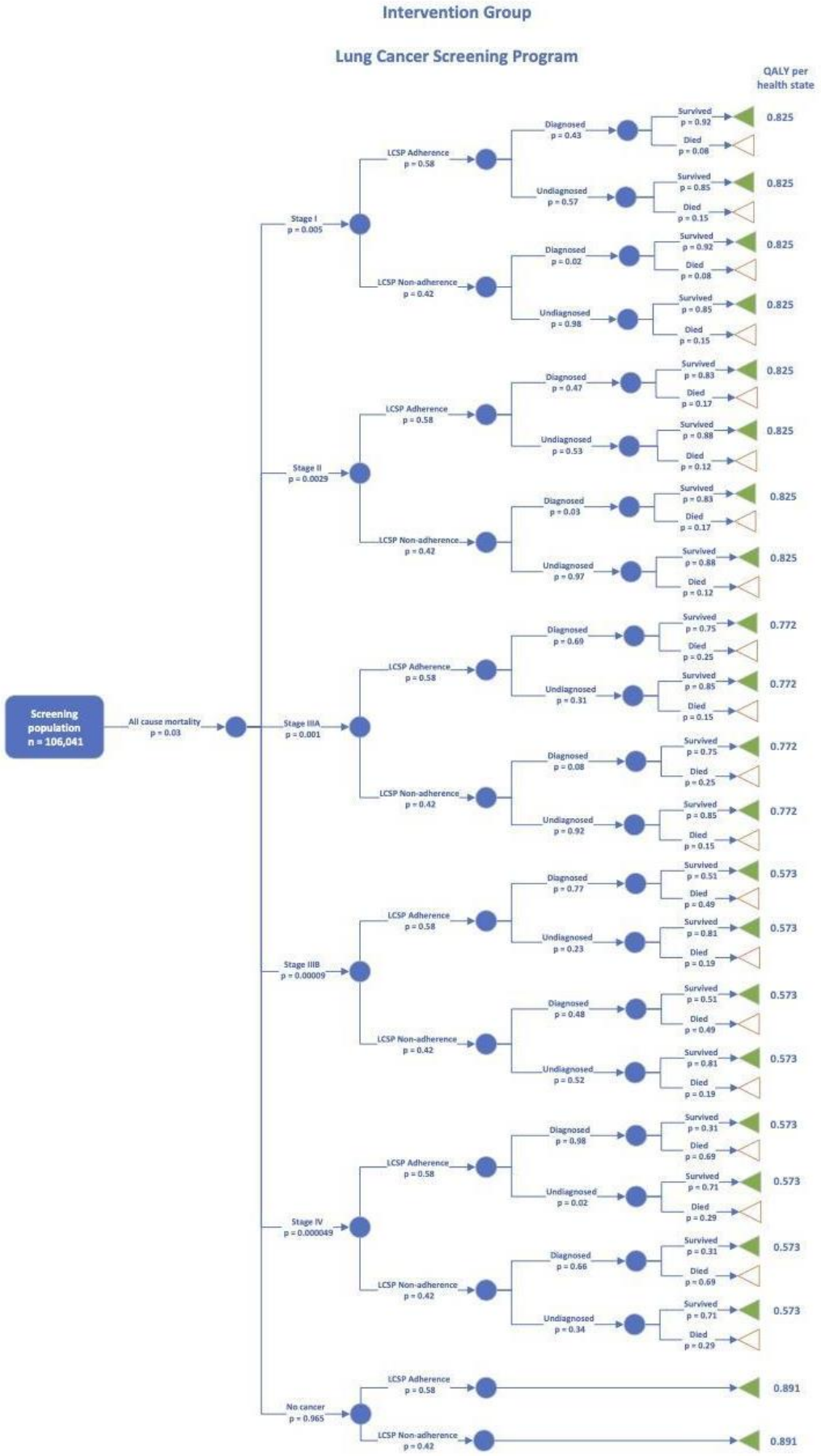
Appendix 2. Summary of Cost-Utility Analysis Studies

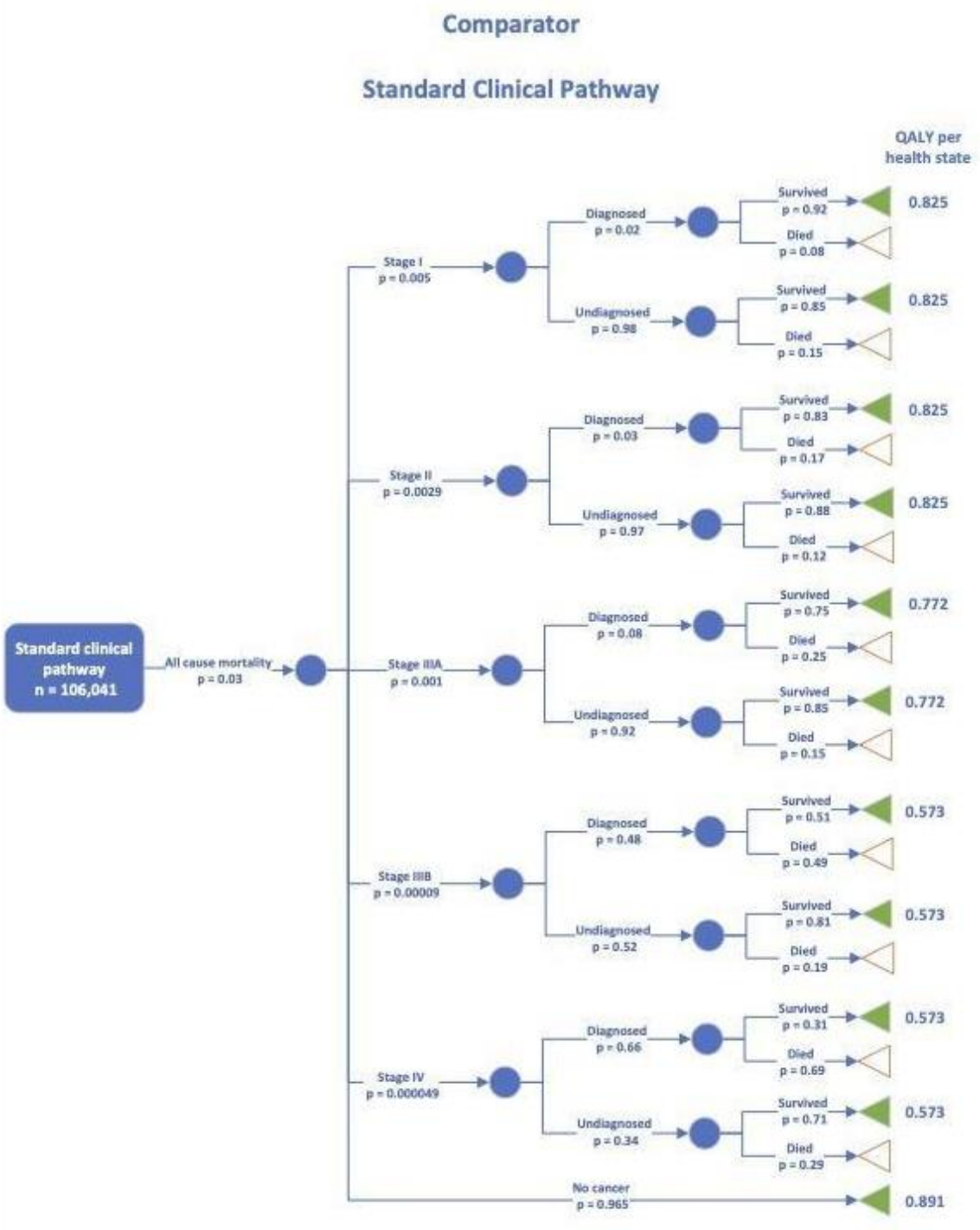
Cost Utility Analysis Overview

Country	Author, Year	Comparator	Intervention (CT schedule)	Data source	Modelling Approach	Perspective	Time Horizon	Discount rate		Cost-effectiveness outcome	QALYs gained per person
								Costs	Benefit		
	Hofer et al. (2018)	No screening	Annual and biennial	RCT	Markov	Payer	15-years	3%	3%	€ 30,291 per QALY (Cost-effective)	0.04
	Field et al. (2016)	No screening	Single	RCT	Decision tree	NHS	Lifetime	3.5%	3.5%	£8,500/QALY (Cost-effective)	0.06
	Snowsill et at. (2018)	No screening	Single, Annual for 3 years, annual, bienniel	RCT	Discreet event simulation	NHS, Personal Social Services	Lifetime	3.5%	3.5%	£28,169/QALY (Not cost-effective)	0.057
	Toumazis et al. (2019)	No screening	Annual and biennial	Literature	Lung cancer outcomes simulator	Single payer/insurer	Lifetime	3%	3%	Indeterminite findings	N/A
	Goffin et al. (2016)	No screening	Annual	RCT	Cancer Risk Management Model	Payer	Lifetime	3%	3%	CAD $52,000-4.8mil/QALY (No cost-effective)	N/A
	Kowada (2022)	No screening	Annual	RCT and literature	Markov	Payer	Lifetime	3%	3%	Cost-effective in Japan Not cost-effective in USA	N/A
	Criss et al. (2019)	No screening	Annual	Literature	Lung cancer outcomes simulator	Health care	45 years	3%	3%	$96,700/QALY (Cost-effective)	0.0065
	Cressman et al. (2017)	No screening	Annual for 3 years	RCT	Markov	Payer	30-years	3%	3%	$20,724 CAD/QALY (Cost-effective)	0.032

Note. References in table

Appendix 3. Decision Tree - Lung Cancer Screening Program and Standard Clinical Pathway


Intervention Group
Lung Cancer Screening Program
QALY per health state
Screening population n = 106,041
All cause mortality p = 0.03
Stage I p = 0.005
Stage II p = 0.0029
Stage IIIA p = 0.001
Stage IIIB p = 0.00009
Stage IV p = 0.000049
No cancer p = 0.965
LCSP Adherence p = 0.58
LCSP Non-adherence p = 0.42
Diagnosed p = 0.43
Undiagnosed p = 0.57
Diagnosed p = 0.02
Undiagnosed p = 0.98
Diagnosed p = 0.47
Undiagnosed p = 0.53
Diagnosed p = 0.03
Undiagnosed p = 0.97
Diagnosed p = 0.69
Undiagnosed p = 0.31
Diagnosed p = 0.08
Undiagnosed p = 0.92
Diagnosed p = 0.77
Undiagnosed p = 0.23
Diagnosed p = 0.48
Undiagnosed p = 0.52
Diagnosed p = 0.98
Undiagnosed p = 0.02
Diagnosed p = 0.66
Undiagnosed p = 0.34
Survived p = 0.92
Died p = 0.08
Survived p = 0.85
Died p = 0.15
Survived p = 0.83
Died p = 0.17
Survived p = 0.88
Died p = 0.12
Survived p = 0.75
Died p = 0.25
Survived p = 0.51
Died p = 0.49
Survived p = 0.81
Died p = 0.19
Survived p = 0.31
Died p = 0.69
Survived p = 0.71
Died p = 0.29
0.825
0.772
0.573
0.891


Comparator
Standard Clinical Pathway
QALY per health state
Standard clinical pathway n = 106,041
All cause mortality p = 0.03
Stage I p = 0.005
Diagnosed p = 0.02
Survived p = 0.92
Died p = 0.08
0.825
Undiagnosed p = 0.98
Survived p = 0.85
Died p = 0.15
0.825
Stage II p = 0.0029
Diagnosed p = 0.03
Survived p = 0.83
Died p = 0.17
0.825
Undiagnosed p = 0.97
Survived p = 0.88
Died p = 0.12
0.825
Stage IIIA p = 0.001
Diagnosed p = 0.08
Survived p = 0.75
Died p = 0.25
0.772
Undiagnosed p = 0.92
Survived p = 0.85
Died p = 0.15
0.772
Stage IIIB p = 0.00009
Diagnosed p = 0.48
Survived p = 0.51
Died p = 0.49
0.573
Undiagnosed p = 0.52
Survived p = 0.81
Died p = 0.19
0.573
Stage IV p = 0.000049
Diagnosed p = 0.66
Survived p = 0.31
Died p = 0.69
0.573
Undiagnosed p = 0.34
Survived p = 0.71
Died p = 0.29
0.573
No cancer p = 0.965
0.891

Appendix 4. Number of Diagnosed Patients in Different Stages After 15 Cycles in the Markov Model and Costs for Each Stage

	Diagnosed Stage I	Diagnosed Stage II	Diagnosed Stage IIIA	Diagnosed Stage IIIB	Diagnosed Stage IV
Current (100%)	160	107	145	284	842
Total Treatment cost for current	45,751,607	29,829,622	62,387,907	156,055,303	644,360,591
LDCT (no adherence 42%)	142	61	61	91	420
Total treatment cost for LDCT (no adherence)	41,436,821	18,656,818	29,991,700	58,742,229	353,228,653
LDCT (Adherence 58%)	1,702	713	330	45	126
Total treatment cost for LDCT (adherence)	413,486,943	182,969,020	136,195,067	24,466,786	103,969,131
Total diagnosed in LDCT intervention	1884	733	391	136	546
Total cost for LDCT (no adherence + adherence)	454,923,764	201,625,838	166,186,767	83,209,014	457,197,784

Appendix 5. Outcomes of Sensitivity Analysis

Assumption	Lower bound	Lower bound % change	Upper bound	Upper bound % change
Adherence +/-50% vs. screening cost -50%	1,174,884	63%	461,901	-36%
Adherence +/- 50%	1,254,396	74%	552,619	-23%
LDCT sensitivity +/-20%	891,280	24%	589,895	-18%
Adherence +/-25%	894,276	24%	619,361	-14%
QALYs	826,410	15%	668,718	-7%
Discount rate 1.5% / 3%	592,726	-19%	729,457	0%
Standard clinical pathway sensitivity +/-50%	716,664	-1%	741,842	3%
LDCT costs +/-50%	636,978	-12%	805,224	12%
Post-diagnosis death rate +/-20%	621,921	-14%	835,779	16%
Treatment costs +/-50%	423,449	-41%	933,856	30%
Worst & Best (+/-50% adherence & LDCT costs & screening costs +/-50%)	262,060	-64%	1,755,439	143%
Adherence +/-50% & treatment costs -50%	664,658	-8%	352,778	-51%
LDCT costs +/-50%, LDCT sensitivity +/-50%	789,112	9%	662,189	-8%

Appendix 6. Undiscounted ICERs From 1 to 30 Cycles

Cycles	Current		LDCT		Incremental Difference		Estimated
	QALYs	Cost	QALYs	Cost	QALYS	Cost	ICER
1	91,356	138,016,095	91,684	410,700,724	328	272,684,630	831,993
5	401,907	465,731,759	403,235	1,665,542,885	1,328	1,199,811,126	903,407
10	691,191	741,763,401	694,812	3,432,588,569	3,621	2,690,825,167	743,199
15	899,614	938,385,132	905,944	5,503,457,083	6,331	4,565,071,950	721,101
20	1,049,820	1,079,795,828	1,058,715	7,853,258,295	8,895	6,773,462,467	761,465
30	1,236,227	1,254,734,490	1,249,034	13,164,586,758	12,807	11,909,852,268	929,938

Appendix 7. Discounted ICERs from 1 to 30 Cycles

Cycles	Current		LDCT		Incremental Difference		Estimated
	QALYs	Cost	QALYs	Cost	QALYS	Cost	ICER
1	87,842	132,707,783	88,157	394,904,543	315	262,196,759	831,993
5	359,694	420,347,048	360,875	1,490,070,491	1,181	1,069,723,443	905,949
10	572,484	623,476,870	575,333	2,779,648,746	2,849	2,156,171,876	756,914
15	698,494	742,356,416	702,972	4,022,510,810	4,478	3,280,154,394	732,470
20	773,135	812,628,685	778,883	5,182,170,894	5,748	4,369,542,209	760,121
30	843,587	878,757,729	850,805	7,142,589,193	7,218	6,263,831,465	867,800

12. Glossary

CADTH	Canadian Agency for Drugs and Technologies in Health
CAR	Cancer Registry
CAR	Danish Cancer Registry
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CEP	Cost-effectiveness plane
CET	Cost-effectiveness threshold
COPD	Chronic obstructive pulmonary airway disease
CPI	Consumer price index
CUA	Cost-utility analysis
DALY	Disability-adjusted life year
DKK	Danish Kroner
DLCR	Danish Lung Cancer Register
DLCR	Danish Lung Cancer Register
DRG-DAGS	Diagnosis-related group database
DSA	Deterministic sensitivity analysis
ECR	Effectiveness-cost ratio
EE	Economic evaluation
ERS	European Respiratory Society
ESR	European Society of Radiology
FCM	Friction-cost method
GDP	Gross domestic product
GP	General practitioner
HCM	Human-capital method
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IPF	Idiopathic pulmonary fibrosis
LCSP	Lung cancer screening program
LDCT	Low dose computed tomography
LLPv2	Liverpool Lung Project risk model
LPR	National Patient Register

LPR	National Patient Register
MFS	Metastasis-free survival
NCCN	National Comprehensive Cancer Network
NELSON	Netherland-Belgian Lung Cancer Screening Trial
NICE	National Institute for Health and Care Excellence
NLST	National Lung Screening Trial
NSCLC	Non-small cell lung cancer
OECD	Organization for Economic Cooperation and Development
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomized control trial
RP	Revealed preference
SACT	Systemic anticancer therapy
SCLC	Small-cell lung cancer
SES	Socioeconomic status
SP	Stated preference
TNM	Tumor node metastasis
TTO	Time trade off
UKLS	United Kingdom Lung Cancer Screening
VAS	Visual-analogue scale
VATS	Video-assisted thoracic surgery
VATS	Video-assisted thoracotomy surgery
WHO	World Health Organization
WTP	Willingness-to-pay