Enhancing the Impact of Lung Cancer Screening:
Assessment of the Performance of Joint Smoking Cessation and Screening Interventions and Personalized Screening Scheduling Using Microsimulation Modeling

by

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Dedication

To my son, Ethan, the ultimate challenge of this dissertation

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Abstract

Lung cancer is the deadliest cancer in the United States. Low-dose computed tomography for lung cancer screening has proven effective in reducing lung cancer mortality and is thus recommended for ever smokers with a considerable smoking history. This dissertation investigated two strategies to refine lung cancer screening (LCS) processes: smoking cessation intervention in the context of LCS and optimal screening schedules for LCS. I utilized a microsimulation modeling approach to quantify the benefits, harms, and costs of various strategies. I considered the screening eligibility criteria under the 2013 US Preventive Services Task Force guidelines: smokers between ages 55 and 80, smoked for at least 30 pack years and former smokers quit within 15 years.

First, I extended the University of Michigan Lung Cancer Natural History and Screening (MichiganLung) model, an established microsimulation model, to compare the effects on mortality of a hypothetical one-time cessation intervention at the first annual screening vs. annual screening alone. I tested the sensitivity of results to different assumptions about screening uptake and cessation efficacy. Across all assumptions, adding a smoking cessation intervention to screening reduced lung cancer mortality and overall deaths compared to screening alone. Our results show that smoking cessation interventions would clearly enhance the net benefits of LCS programs.

Second, in collaboration with colleagues from the National Cancer Institute Smoking Cessation at Lung Examination Consortium, we conducted a cost-effectiveness analysis for

cessation interventions at the first screen plus annual screening using the MichiganLung model. We considered five cessation interventions, including pharmacotherapy only, or pharmacotherapy with web-based, telephone, individual, or group counseling. Cost-effective cessation strategies included pharmacotherapy with web-based, telephone, or individual counseling. All smoking cessation interventions delivered with LCS were likely to reduce lung cancer mortality and result in life-years gained at reasonable costs. The choice of cessation intervention for screening clinics should be guided by practical concerns such as staff training and availability.

Third, although annual LCS is currently recommended, a less intensive schedule may be preferable for low-risk individuals. I utilized a risk-threshold method to determine optimal screening schedules based on individual lung cancer risk, past screening results and other risk factors. Using the MichiganLung model, I compared lung cancer outcomes from adaptive screening schedules to regular (non-adaptive) triennial, biennial, and annual screenings. Adaptive screening schedules had a better benefit-to-harm ratio and were more efficient than regular screening schedules. Individual lung cancer risk and preferences play an important role in the performance of LCS. These findings support the adoption of patient-centered decision-making processes and individualized LCS strategies.

Finally, I evaluated the cost-effectiveness of adaptive and regular (non-adaptive) schedules for LCS using the MichiganLung model results. I identified 9 dominant strategies, with 8 being adaptive schedules while 1 being annual screening. Compared with no screening scenario, all strategies had a cost to QALY ratio under $50,000. Compared incrementally, seven out of the eight dominant adaptive schedules were cost-effective under the $100,000 willingness-to-pay threshold, whereas annual screening had an incremental cost to QALY ratio over

$120,000. Hence, under a fixed budget healthcare system, adaptive schedules may provide better "value for the money."

Overall, this dissertation identified two strategies that could enhance the impact of LCS by maximizing the net benefits and cost-effectiveness. It furthermore demonstrates the potential for mathematical modeling to translate risk estimates and other epidemiological data into clinically meaningful recommendations.

Chapter I

Introduction

1.1 Lung cancer burdens and cancer control strategies

Lung cancer is the second most common cancer among men and women in the United States, with new cases estimated to be 119,000 for men and 116,600 for women in 2021, following prostate cancer (248,530 new cases in 2021) and female breast cancer (281,550 new cases in 2021).[1] Although its incidence is half that of prostate and breast cancer, lung cancer is the most common cause of cancer deaths, with the mortality rate twice that of breast and prostate cancer.[1] The high lung cancer mortality is primarily due to the fact that the 5-year survival rate is only 21%, whereas it is 90% for breast cancer and 89% for prostate cancer.[1] So what cancer control strategies could be implemented to relieve the lung cancer burden in the United States?

Cancer prevention strategies are broadly classified into three groups—primary, secondary and tertiary prevention.[2] Primary prevention of cancer usually involves interventions that prevent or reduce the risk of the onset of cancer and target risk factor exposures on healthy populations. Some notable examples of primary prevention include anti-smoking education in schools, smoking cessation programs, and HPV vaccination. Secondary prevention of cancer refers to efforts to detect cancers at earlier stages (premalignant or early malignant stages), before having noticeable signs and symptoms of disease. Secondary prevention occurs predominantly through cancer screening and identification of groups at high risk of cancer. Some examples of early

detection through screening are colonoscopy screening for colorectal cancer, mammograms for breast cancer, low-dose computed tomography (LDCT) for lung cancer, and the prostate-specific antigen (PSA) test for prostate cancer. Tertiary prevention involves managing disease post diagnosis to slow or stop disease progression or recurrence through interventions such as treatment, rehabilitation, and follow-up care.

While treatment interventions are critical, it is important to focus our lung cancer prevention efforts on primary prevention and early detection for three reasons. First, more than 80% of lung cancer cases can be attributed to smoking and thus by reducing smoking prevalence, we can expect a great reduction in lung cancer incidence and mortality (primary prevention).[1,3] Second, lung cancer screening using the LDCT scan is an effective intervention, which enables early detection of lung cancer and thus improves treatment outcomes, reducing lung cancer mortality.[4] Last, without screening, lung cancer is usually diagnosed at an advanced stage where treatments are limited and 5-year survival is low.[1] Therefore, it is essential to prevent or detect lung cancer at an early stage.

1.2 Smoking and lung cancer

Tobacco smoking is a known risk factor for several cancers, such as lung, larynx, and esophageal cancer.[1] Multiple chemicals in cigarettes and combustible tobacco are known carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines.[5] These chemicals induce cancer through two major pathways. Continuous exposure to carcinogens in tobacco products leads to the formation of DNA adducts, which eventually result in persistent DNA mutations, if the DNA adducts are not repaired and enter the replication cycle (initiation).[5] If the mutations occur in oncogenes or tumor-suppressor genes, cancer may eventually develops (malignant conversion). Furthermore, the carcinogens may bind

directly to the crucial cellular receptors, leading to reduced apoptosis, increased angiogenesis and cell transformation, forming a favorable cellular environment for premalignant or malignant cells to grow (promotion).[5]

An estimated 82% of lung cancer can be attributed to smoking, which is the highest proportion among all cancers.[1] Although the risk of lung cancer is higher among smokers than non-smokers, the strength of the association differs by histologic types.[6] Lung cancer can be broadly classified into two histologic groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), where NSCLC are further categorized as squamous cell lung cancer, adenocarcinoma, large cell lung cancer, and other types. SCLC and squamous cell lung cancer are thought to be exclusively due to smoking, while adenocarcinoma is less associated with smoking.[6]

The smoking prevalence in the United States has been decreasing over the last 50 years, which has been followed by a reduction in lung cancer incidence and mortality.[3] Lung cancer mortality has been projected to decrease by 79% from 2015 to 2065 due to the past and expected continuous decline in smoking.[3] The population attributable fraction of lung cancer due to smoking has also been projected to decrease from around 80% in 2015 to 50% in 2065.[3] The histologic distribution of lung cancer cases has also changed. With the decrease in smoking prevalence, the incidence of SCLC, large cell lung cancer, and squamous cell lung cancer has been decreasing, overall and proportionally.[6,7] However, the incidence of adenocarcinoma has been on the rise since the 1980s, and has become the most common type of lung cancer in both males and females accounting for over 30% of all cases in 2015.[6–8]

1.3 Lung cancer screening in the United States

Besides tobacco control, another effective control strategy for lung cancer is low-dose computed tomography (LDCT) screening. In 2011, the National Lung Screening Trial (NLST) concluded that three rounds of LDCT screening resulted in a 20% reduction in lung cancer mortality compared to chest x-ray screening for the study population aged between 55 to 74, who smoked no less than 30 pack years and quit no more than 15 years ago.[4] In 2013, based primarily on the NLST results and supported by Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Working Group (LWG) decision analyses, the United States Preventive Services Task Force (USPSTF) recommended annual lung cancer screening for ever smokers between the ages of 55 and 80, with at least 30-pack years of smoking history and no more than 15 years since quitting.[9,10] Similarly in 2015, the Center for Medicare and Medicaid Services (CMS) recommended coverage of annual lung cancer screening under Medicare, with eligibility criteria differing slightly from the USPSTF's (stopping at age 77 instead of 80).[11] In 2020, the Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) showed a 24% and 33% reduction in lung cancer mortality among males and females respectively after four rounds of volume-based LDCT screening.[12] The NELSON trial had a different screening eligibility from NLST, being aged 50 to 74 at baseline, quit no more than 10 years ago, and smoked more than 10 cigarettes a day for more than 30 years or more than 15 cigarettes a day for more than 25 years.[12] In 2021, supported by the NELSON trial and other epidemiological studies and informed by the updated CISNET modeling results, the USPSTF updated its lung cancer screening recommendation by extending the eligibility population to include 50 to 54 years old individuals and those who had smoked 20 to 29 pack years.[13,14]

1.4 Smoking cessation in the lung cancer screening setting

In addition to directly reducing lung cancer mortality and increasing life expectancy through earlier detection and initiation of treatment, lung cancer screening has been hypothesized to be a teachable moment, where current smokers might be motivated to quit smoking.[15] Cessation counseling and referral to cessation interventions have been mandated to be a key component of the shared decision-making appointment prior to lung cancer screening.[11] Nevertheless, the best way to deliver the cessation intervention in the screening setting, its costs and effectiveness, and the synergic effects of cessation interventions and lung cancer screening remain unclear. The SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration has eight clinical trials underway to answer these questions.[15–18] While we await the clinical trial results, modeling studies have helped us understand the impact of integrating smoking cessation intervention into lung cancer screening under various assumptions.[19–22]

1.5 Lung cancer natural history and screening model

Simulation models of cancer natural history have been shown to be valuable in evaluating and determining optimal cancer prevention and control strategies. Recent example includes cost-effectiveness analysis of risk-based lung cancer screening,[23] assessment of different breast cancer screening intervals among low-risk women,[24] and evaluation of lifetime benefits and harms of tailored prostate screening strategies by prostate-specific antigen level.[25] Furthermore, results of these modeling studies could aid policy making in public health sectors or federal governments. Supported by the simulation results from the CISNET models, the USPSTF updated its recommendations of lung and colorectal cancer screening in 2021,[13,26] cervical screening guidelines in 2018,[27] and is in the process of updating the breast cancer screening recommendations.[28]

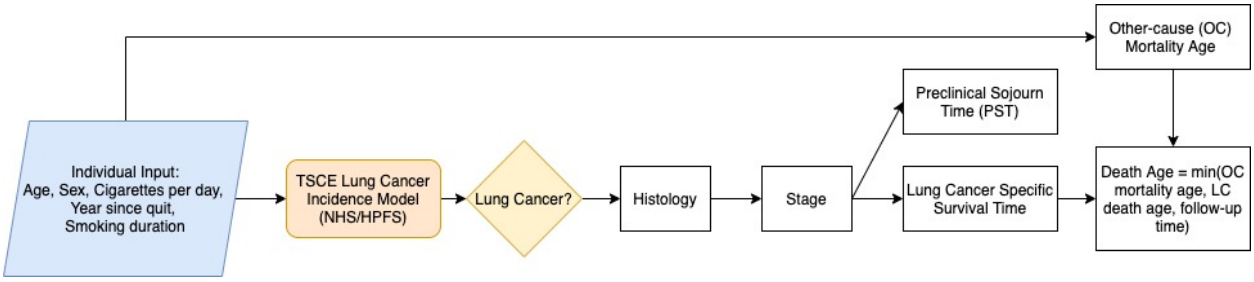
All aims in this dissertation rely heavily on lung cancer natural history and screening modeling. I use a previously validated microsimulation model—the CISNET MichiganLung model[13,19,20,23,29,30]—to simulate lung cancer incidence and outcomes (Figure 1.1). The MichiganLung model is a discrete-time microsimulation model that consists of two components—natural history and screening. The natural history component consists of several sub-models: incidence component, histology component, stage component, preclinical sojourn time component, and survival component. Each component was developed independently using relevant data sources, and then all components were integrated into MichiganLung to capture the whole natural history of lung cancer. Using individual smoking histories as input, I use a version of the Two-Stage Clonal Expansion model calibrated to the Nurses' Health Study and Health Professionals' study[31] to obtain age-specific lung cancer incidence rates and determine the age at clinical diagnosis of lung cancer if any. Lung cancer histology is then generated based on sex, age at diagnosis, and smoking history, using a multinomial logistic regression model fitted to the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial control arm data.[29] Lung cancer stage is assigned based on the distribution by sex and histology, obtained from the Surveillance, Epidemiology, and End Results (SEER) Program lung cancer incidence data.[32] Then lung cancer-specific survival given histology and stage is generated using a survival model with cure probability which was fit to the SEER lung cancer survival data using the CanSurv software.[33] The length of stage-specific preclinical sojourn time given histology and stage were generated using sojourn time distributions that were calibrated to the NLST and PLCO data.[34] Given such detailed history, especially the onset and progression of preclinical cancer, I am able to simulate the impact of lung cancer screening and different screening strategies on lung cancer-related health outcomes. The model uses estimates of the sensitivity and specificity per LDCT screen by

lung cancer histology and stage to simulate the lifetime impact of annual LDCT screening for individuals in the US population.[34] The model is able to reproduce the stage shift and reduction in lung cancer mortality after three rounds of LDCT screening as observed in NLST.[29] The model has been used to simulate the population impact of different screening strategies for the US population,[10,23,29,30,35] including the relative differences of current recommendations versus risk-based screening strategies,[23] the impact of patient preferences on benefits from lung cancer screening,[29] as well as the cost-effectiveness of strategies varying the age at stopping screening.[30]

1.6 Specific Aims

In the following chapters, I examine different strategies to improve lung cancer screening, aiming to increase its benefits while reducing its potential harms, and evaluate the effectiveness and cost-effectiveness of these strategies. In Chapter II, I use an established CISNET model to estimate the reductions in lung cancer, all-cause deaths, and life-years gained with cessation interventions delivered at the point of lung cancer screening vs. screening only. I use the model to assess the magnitude of cessation benefits under varying assumptions of lung screening uptake and cessation efficacy. In Chapter III, I use the model to estimate the benefits, costs, and cost-effectiveness of the delivery of five different types of cessation interventions at the point of lung cancer screening. In Chapter IV, I adapted a risk-threshold method, an analytic approach developed by Zelen et al.,[36] to identify optimal schedules for lung cancer screening accounting for various risk factors and life expectancy. I then assess the cost-effectiveness of efficient screening schedules identified in Chapter IV, compared with current lung cancer screening guidelines (Chapter V). The dissertation concludes with a discussion of the implications of the findings and suggestions for additional work.

Figure 1.1. Lung cancer natural history simulation in the MichiganLung model


Other-cause (OC) Mortality Age
Preclinical Sojourn Time (PST)
Individual Input:
Age, Sex, Cigarettes per day,
Year since quit,
Smoking duration
TSCE Lung Cancer Incidence Model (NHS/HPFS)
Lung Cancer?
Histology
Stage
Lung Cancer Specific Survival Time
Death Age = min(OC mortality age, LC death age, follow-up time)

Chapter II

Potential Impact of Cessation Interventions at the Point of Lung Cancer Screening on Lung Cancer and Overall Mortality in the United States

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2.1 Introduction

Despite recent progress, lung cancer is the second most common cancer in women and men, and the leading cause of cancer death in the United States.[1,37] At least 80% of lung cancers could be averted by avoiding smoking initiation.[38] Among those who already have a long history of cigarette use, lung cancer screening can reduce lung cancer mortality.[12,39,40] Based on this evidence, lung cancer screening using low-dose computed tomography scans is now recommended by the United States Preventive Services Task Force (USPSTF) for adults aged 55-80 with ≥30 pack-year smoking history who currently smoke or quit within the past 15 years.[9]

In addition to directly increasing life expectancy through earlier stage at detection and initiation of treatment, lung cancer screening has been hypothesized to be a teachable moment, where current smokers might be motivated to quit smoking.[15,41–43] Cessation counseling and referral to cessation interventions have been recommended as a key component of lung screening

programs[9,11] because smoking cessation decreases lung cancer as well as other tobacco-related morbidity and mortality risk. Nevertheless, little is known about the efficacy of cessation interventions in the screening setting. There are clinical trials underway to fill this gap, [15–18,44] but results are not expected for several years.[45] Further, little is known about the potential synergistic effects of joint screening and smoking cessation programs on population lung cancer and tobacco-related morbidity and mortality rates.

In this chapter, we used an established Cancer Intervention and Surveillance Modeling Network (CISNET) model to estimate reductions in lung cancer, all-cause deaths, and life-years gained with cessation interventions delivered at the point of lung cancer screening vs. screening only. We tested the magnitude of cessation benefits under varying assumptions of lung screening use and cessation efficacy. The results of this study are intended to provide guidance on the conduct of future research evaluating specific interventions, including costs and feasibility of their implementation and dissemination.

2.2 Methods

We used an established CISNET lung cancer microsimulation model to portray the process of smoking initiation and cessation, the impact of cessation and screening on lung cancer incidence and mortality and all-cause mortality. The model has been described in detail elsewhere.[29] Briefly, the model uses individual US smoking histories as input to simulate random lung cancer outcomes, including the onset of preclinical and clinical lung cancer, and survival or death in the absence of screening. The model then simulates the impact of interventions such as smoking cessation or screening on individual smoking and lung cancer outcomes.

2.2.1 Population and the CISNET Smoking History Generator (SHG)

The smoking history generator (SHG) is a micro-simulation model that produces US cohort-specific smoking histories by age and gender for cohorts born from 1864 to present.[3,46,47] The SHG has been shown to reproduce the actual history of smoking in the US.[46] The SHG simulates individual smoking histories (number of daily cigarettes smoked per age) and age at death from competing causes of death using US estimates of smoking initiation, cessation, intensity (cigarettes per day), and mortality rates by smoking status. To accomplish this, the model used data from the IPUMS Health Surveys, a harmonized version of the National Health Interview Survey (NHIS) from 1965 to 2015,[48] the Human Mortality Database (HMD),[49] as well as data on lung cancer mortality from the Cancer Prevention Study (CPS)-I [50] and the CPS-II.[51]

The modeling of age-specific smoking intensity is used to simulate individual cumulative smoking exposure (pack-years) to determine screening eligibility.

We utilized the SHG to generate smoking histories of 1 million men and 1 million women for the 1950 and 1960 US birth-cohorts to represent of smoking patterns of the population. We picked the sample size based on earlier work that suggests that 1 million individuals are sufficient to obtain stable estimates. The 1950 and 1960 birth cohorts were chosen since they are now in the middle of their screening eligibility according to current guidelines (70 years old for 1950 and 60 years old for 1960 in year 2020) and they are representative of different periods of the tobacco epidemic (higher smoking prevalence for 1950 vs. decreasing prevalence for 1960).

2.2.2 University of Michigan Lung Cancer Natural History and Screening Model

The UM Lung Cancer Natural History and Screening (*MichiganLung*) Model is a discrete-state microsimulation model that simulates the natural history of lung cancer (onset,

histological type, stage progression, clinical detection and mortality or survival) and the outcomes of LDCT screening and any resulting follow-up and treatment intervention.[23,29,30] The model consists of three main components: natural history, screening and cost/utilities. The model simulates individual preclinical and clinical lung cancer histories and outcomes per CT screen and has been shown to reproduce the relatively short-term outcomes of a few rounds of CT screening in randomized control trials by arm, lung cancer histology and stage.[29,52] The model uses estimates of the sensitivity and specificity per CT screen by lung cancer histology and stage[34] to simulate the lifetime impact of annual CT screening for individuals in the US population.[23,30]

In this chapter, the *MichiganLung* model was used to simulate lung cancer and screening outcomes among screen-eligible individuals from the 1950 and 1960 birth cohorts under different scenarios of screening uptake and under different cessation intervention rates.

2.2.3 Modeling cessation

A hypothetical smoking cessation intervention following the first screen was incorporated into the *MichiganLung* model (see Appendix Figure A.1). Every current smoker undergoing LDCT screening for the first time undergoes a one-time hypothetical smoking cessation intervention. An individual going through the hypothetical cessation intervention was assumed to have a probability of quitting due to the intervention.

If the individual quits, the age- and gender-specific other-cause mortality based on the updated smoking history is generated using the SHG mortality rates by smoking status. In addition, the individual's lung cancer natural history following a cessation intervention is re-simulated with the following considerations: 1) Individuals who did not have lung cancer in the no-screening scenario but gained extra life years due to quitting smoking earlier might get lung

cancer during the additional years of life; 2) individuals who were diagnosed with lung cancer in the no-screening scenario, and quit smoking more than 2 years before the onset of their lung cancer may have their lung cancer incidence age delayed or completely eliminated based on their reduced lung cancer risk. If the age of lung cancer incidence is delayed, histology and stage progression are updated accordingly; 3) individuals who were diagnosed with lung cancer in the no-screening scenario but quit smoking less than 2 years before their lung cancer diagnosis keep their original lung cancer age at diagnosis and lung cancer natural history (histology and stage progression), but have improved other cause mortality.

2.2.4 Outcomes and scenarios

We considered three main outcomes: lung cancer deaths averted, premature all-cause deaths averted (deaths delayed) and life years gained (LYG). We compared these as well as the number of people screened and the number of individuals going through the cessation intervention for different scenarios of screening uptake (percentage of eligible individuals screened) and of the probability of quitting due to the intervention. In particular, we evaluated the impact of varying screening uptake from 5% to 100% in 5% increments, and varying the probability of quitting due to the intervention from 0% to 30% in 2.5% increments informed by the estimated efficacy of current trials,[53–56] and a recent meta-analysis which focused on studies of smokers likely to be eligible for screening based on age and smoking history.[45]

We provide results per 100,000 individuals at age 45. Since the proportion and characteristics of screen-eligible individuals varies by birth cohort and by scenario, our results are calculated "per population" (including both screened and unscreened individuals) rather than "per screened population" so that they are comparable across cohorts.

2.3 Results

As individual's age, the proportion that is both a current smoker and eligible for screening decreases (Figure 2.1). Approximately 10% and 14.9% of the population are screening-eligible current smokers at age 55, decreasing to about 2.7% and 3.5% at age 80 in the 1960 and 1950 birth cohorts, respectively.

Overall, the magnitude of projected gains from smoking cessation interventions depends on screening uptake and the probability of quitting as a result of the intervention. For screening uptake rates ranging from 10-100%, the percent reduction in lung cancer deaths with cessation vs. screening alone ranged from 3% to 52% with cessation probabilities from 5% to 25% (Table 2.1), while the percent increase in life years varied from 40% to over 200% (Table 2.2).

For example, for the 1950 birth-cohort, assuming a 30% screening uptake, the number of lung cancer deaths averted per 100,000 population would increase from 244 in the no-cessation intervention scenario to 278 (14% higher) for an intervention with a 10% probability of quitting. The number of deaths averted would increase to 350 (43% higher vs. no-cessation) for an intervention with a 25% probability of quitting. Similarly, under a cessation intervention with 5% quit probability, the number of lung cancer deaths averted would increase from 93 per 100,000 population under a 10% uptake scenario to 881 per 100,000 (843% higher) under a 100% uptake scenario. In general, the number of lung cancer deaths averted for the 1950 birth-cohort is about twice that for the 1960 birth-cohort in all scenarios.

The number of LYG also increases with both screening uptake and the probability of quitting. For instance, for the 1950 birth-cohort, assuming a 30% screening uptake, the number of LYG per 100,000 population would increase from 3,645 in the no-cessation intervention scenario to 6,580 (80% higher) with an intervention with 10% quit probability. Similarly, under a

cessation intervention with 5% quit probability, the number of LYG would increase from 1,746 per 100,000 population screened under a 10% uptake scenario to 17,415 per 100,000 (897% higher) under a 100% uptake scenario. In general, the amount of LYG is about 65-80% higher for the 1950 birth-cohort.

Figure 2.2 shows cumulative LYG (left), lung cancer deaths averted (middle), cumulative all-cause deaths delayed by age (top right), and age-specific all-cause deaths delayed (bottom right) for different quit probabilities (0%, 5%, 10%, 15%, 20%, 25%) under a 30% uptake scenario. The top panels correspond to the 1950 birth-cohort and the bottom panels to the 1960 birth-cohort. Cumulative life-years gained and lung cancer deaths averted increase as a function of age, with more gains with higher cessation probability. In contrast, cumulative deaths averted from all causes increase, but then peak around age 80 and then decrease since everyone in the simulation eventually dies. The age-specific all-cause deaths figure shows how premature deaths are delayed by screening and cessation programs by about two decades. Figure 2.3 shows heat maps of lifetime cumulative LYG (left), lifetime cumulative lung cancer deaths averted (middle), and deaths from all causes delayed by age 80 (right) for screening uptake ranging from 5-100% and quit probabilities ranging from 0-30%. The top panel shows the heat maps for the 1950 birth-cohort and the bottom panels for the 1960 birth-cohort. We can see that for medium to high levels of screening uptake, the quitting probabilities have a considerable impact on the resulting life-years gained and delayed deaths from all causes by age 80 (nonlinear pattern), but that they have a lesser effect on lung cancer deaths averted (horizontal linear pattern).

2.4 Discussion

This model-based analysis provides clinical and policy relevant data on the potential mortality impact of mandated delivery of smoking cessation interventions to US smokers at the

time of lung cancer screening. Providing a one-time smoking cessation intervention to current cohorts of adults eligible for lung cancer screening is projected to save considerable additional lives beyond those expected with annual low-dose computed tomography screening alone. We found that even a modest quit rate results not only in fewer lung cancer deaths, but also in a large increase in life years gained and delays in overall mortality. These incremental benefits occur largely because smoking cessation not only reduces the rates of developing lung cancer, but also substantially extends life due to a reduction of other tobacco-related conditions such as cardiovascular disease, chronic obstructive pulmonary disease and other smoking-related cancers.[38] This conclusion was robust across a wide variety of assumptions, but the absolute magnitude of the overall population benefits of providing cessation at the time of screening is expected to vary considerably based on the dynamic effects of the joint combinations of cohort-and-age-specific smoking rates, screening uptake, and the probability of quitting after cessation interventions.

From the clinical perspective, these results underscore the importance of provider discussions of smoking cessation in visits for decision making about lung cancer screening. One provider barrier to universal offering of smoking cessation to current smokers eligible for screening is the lack of evidence regarding effective interventions in the context of lung screening.[15,45] There are few trials to date in the lung cancer screening setting, but early results demonstrated quit ranges ranging from 1.4% to 20%.[53–56] The National Cancer Institute's Smoking Cessation at Lung Examination (SCALE) initiative includes eight trials designed to provide a robust evidence base of feasible, scalable approaches to providing smoking cessation, including combinations of pharmacotherapy, in-person counseling, and telephone counseling.[15–18,44] The NCI-Lung Population-based Research to Optimize the Screening PRocess (PROSPR)

initiative is now also evaluating the implementation of screening-based cessation programs across diverse health systems.[57] However, the results of these trials and studies will not be available for several years.[45] Until then, our results suggest that even modestly successful interventions will provide meaningful health benefits beyond those obtainable with screening alone.

There are also several policy implications of our findings. First, while the US Preventive Services Task Force recommends and the Centers of Medicare and Medicaid Services (CMS) mandates inclusion of smoking cessation to all current smokers undergoing lung cancer screening in the US,[9,11] formal integration of cessation programs is not yet required for certification or reimbursement of lung cancer screening services. CMS does require a shared decision-making visit for reimbursement of the screening exam. Smoking cessation is expected to be discussed during this visit.[11] There is wide variability in the content of these shared decision-making visits across health systems and providers.[58] For instance, a recent study found that provider discussion of smoking cessation was often limited by short visit durations and patients' resistance and lack of interest, with referral rates to a local cessation clinic or quitline below 25%.[58] Optimal integration of cessation programs into the screening process is a challenge, as the intervention of choice will likely vary for a given setting and population, area resources, and the screening workflow process.[57] Further research regarding the effectiveness and cost-effectiveness of cessation interventions at the point of screening would help provide the basis for the development of standards and best practices for cessation programs within lung screening. Guidelines similar to those by the Joint Commission for inpatient smoking cessation might also be useful to accelerate the inclusion of effective cessation service delivery into screening programs.[59]

Another policy-level consideration is that the uptake of lung cancer screening among the screen-eligible population has been low in the US, varying widely by region, with estimates ranging from 18% in Florida to 7% in Nevada.[60] Our results indicate that even with a 20% screening rate, which seems achievable in the near future, lung cancer screening could result in 158 lung cancer deaths averted per 100,000 for the 1950 birth cohort compared to no screening. Different interventions are being proposed to improve screening uptake, including education programs to increase physician's knowledge of screening recommendations, and interventions to increase patient awareness and facilitate access for hard-to-reach populations.[61] Given the high costs of lung cancer care, it is possible that investments in interventions to increase screening uptake (and increase early stage diagnosis) would be cost-effective, especially given the high costs of new treatment paradigms for more advanced stage lung cancer.[62] However, even if lung cancer screening were used annually by 100% of eligible adults, and saved lung cancer care costs, screening will not affect other tobacco-related morbidity and mortality. Thus, complementing screening with cessation interventions is needed to maximize its potential benefits.

Overall, our model analysis contributes to the growing clinical and policy discussions about how to maximize the potential of lung cancer screening and tobacco control in the US.[63–66] Previous modeling analyses have assessed the cost-effectiveness of lung screening with and without cessation programs under different assumptions of the efficacy of the cessation intervention and all found that adding cessation to lung screening improved outcomes.[67–69] Villanti and colleagues found that adding a cessation intervention with 1.25-5% quit rates could improve the cost-effectiveness of lung screening in the US by 20-40%.[67] In an analysis of the Canadian population Goffin et al evaluated the cost-effectiveness of annual and biennial lung

screening with and without a single smoking cessation intervention.[49,50] They found that adding a cessation intervention with a 22.5% quit probability would improve the cost-effectiveness of annual and biennial lung screening by 50% and result in considerable gains in quality adjusted life years. Our study extends these results by considering background cessation rates that vary by age, cohort and sex, a wider range on the quit probabilities and screening uptake, and using a detailed model of lung cancer natural history, screening and cessation.

Our simulation modeling is also useful to illustrate how the dynamic balance between smoking patterns, screening use, and cessation intervention effectiveness in the screening setting might impact overall population mortality rates. The success of tobacco policies and changes in lifestyle has led to a steady decline in smoking rates over the past four to five decades.[3] Based on these trends, smoking cessation (and lung screening) had greater benefits in the 1950 birth-cohort because they had higher smoking prevalence at older ages than the 1960 cohort. It will be important to re-evaluate our results in future cohorts as smoking patterns evolve and possibly shift into other tobacco products.[70] Modeling provides a flexible virtual laboratory platform to quickly project the impact of the changing landscape of tobacco control and targeted lung cancer therapy on the overall population lung cancer and tobacco-related disease mortality.

This modeling research used a well-established CISNET lung cancer natural history simulation model to synthetize large national studies of smoking patterns, trials screening effects, and SEER population-based cancer registry data. This model has been used previously to extrapolate the benefits of lung screening from randomized controlled trials to the US population, and the results of the model used in this study are similar to the other CISNET lung models.[23,29,30] The model has also been used to simulate the population impact of different screening strategies for the US population,[23,29,30] including the relative differences of current

recommendations versus risk-based screening strategies,[23] the impact of patient preferences on benefits from lung cancer screening,[29] as well as the cost-effectiveness of strategies varying the age at stopping screening.[30] The model has external validity as it reproduces the short-term outcomes of a few rounds of computerized lung cancer tomography screening in randomized control trials by arm, lung cancer histology and stage.[29,52] Finally, we used a validated model of individual smoking histories in the US that has been shown to reproduce the history of smoking by birth-cohort for the US population.[3,46,47]

Despite use of robust CISNET models and large national datasets, there are several caveats that should be considered in evaluating our results. First, we did not evaluate cost-effectiveness of joint screening and cessation programs. This will be important in our future modeling research to evaluate the impact of specific interventions. Relatedly, we modeled only a single cessation intervention at the time of first screen. In practice, it is likely that once cessation programs within lung screening are established, these will become available to current smokers at the time of each annual screen. Thus, our results are likely a conservative estimate of the potential impact of effective joint cessation and screening interventions. Finally, we restricted our analyses to two single birth cohorts of the US population. While these two cohorts are representative of the current eligible population, simulation of the whole US population is needed to project the actual impact that these interventions will have on US lung cancer and tobacco-related mortality.

In summary, our findings highlight the need for effective joint smoking cessation interventions to maximize the population benefits of lung screening. Effective cessation interventions at the point of screening could also save lives due decreases in other tobacco-related diseases as a consequence of smoking cessation. The future population impact of

providing cessation with lung cancer screening is expected to be dynamic based on changing trends in tobacco use and products, the reach of screening, and the ability to fully integrate cessation and screening into clinical workflow.

2.5 Tables and figures

Table 2.1. Lung cancer deaths averted per 100,000 population at age 45 (by selected cessation probabilities and uptake) for 1950 and 1960 birth cohorts

Birth Cohort 1950						
Screening uptake	*Probability of Cessation due to Intervention*					
	0%	5%	10%	15%	20%	25%
100%	807	881	955	1,029	1,090	1,173
70%	549	623	665	712	758	815
50%	402	436	479	516	548	591
30%	244	257	278	303	337	350
20%	158	177	189	195	212	231
10%	80	93	94	107	108	118
Birth Cohort 1960						
	0%	5%	10%	15%	20%	25%
100%	425	453	496	538	576	612
70%	298	323	346	372	408	435
50%	211	227	251	271	286	306
30%	131	135	156	162	172	184
20%	81	95	102	110	117	123
10%	42	46	49	54	59	61

Table 2.2. Life-years gained per 100,000 population at age 45 (by selected cessation probabilities and uptake) for 1950 and 1960 birth cohort

Birth Cohort 1950						
Screening Uptake	*Probability of Cessation due to Intervention*					
	0%	5%	10%	15%	20%	25%
100%	12,083	17,415	22,500	27,456	32,573	37,895
70%	8,243	12,137	15,639	19,352	22,781	26,419
50%	6,010	8,584	11,263	13,702	16,418	19,003
30%	3,645	5,116	6,580	8,286	9,913	11,400
20%	2,355	3,438	4,398	5,432	6,437	7,413
10%	1,203	1,746	2,311	2,849	3,275	3,767
Birth Cohort 1960						
	0%	5%	10%	15%	20%	25%
100%	6,460	9,540	13,105	16,377	19,436	22,986
70%	4,480	6,785	9,068	11,484	13,766	16,229
50%	3,228	4,833	6,551	8,218	9,887	11,515
30%	1,998	2,901	4,034	4,912	5,913	6,830
20%	1,256	1,926	2,641	3,362	3,854	4,614
10%	677	986	1,313	1,619	1,984	2,262

Figure 2.1. Screening eligibility by age and smoking status for birth cohort 1950 (left) and 1960 (right) under the current USPSTF guideline

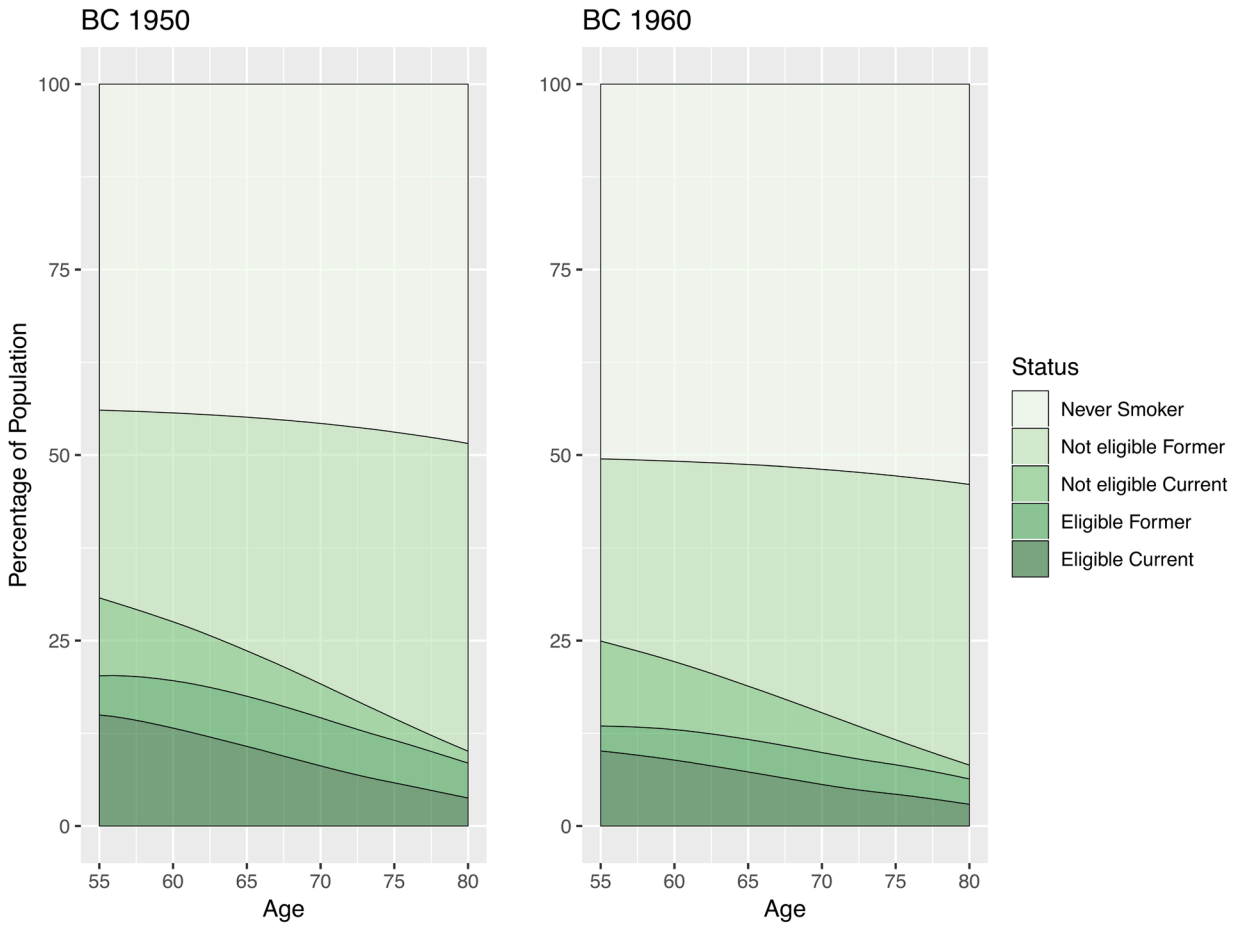


Figure 2.2. Cumulative life-years gained (left), cumulative LC deaths averted (middle), cumulative deaths averted (top right), and deaths delayed (bottom right) with the probability of quitting being 0%, 5%, 10%, 15%, 20% and 25% under screening uptake of 30% for 1950 (top panel) and 1960 (bottom panel) birth cohorts. All results are presented per 100,000

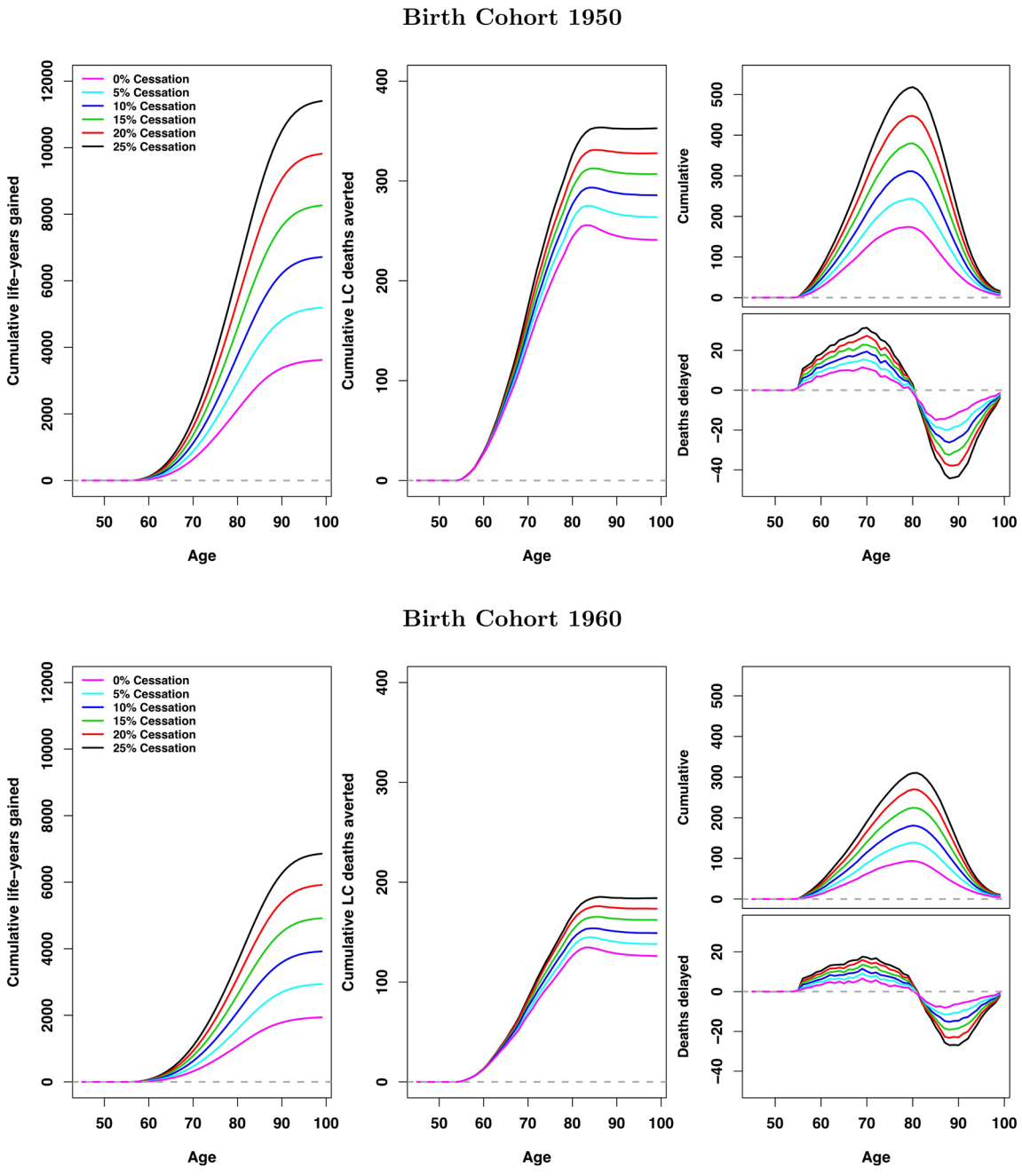
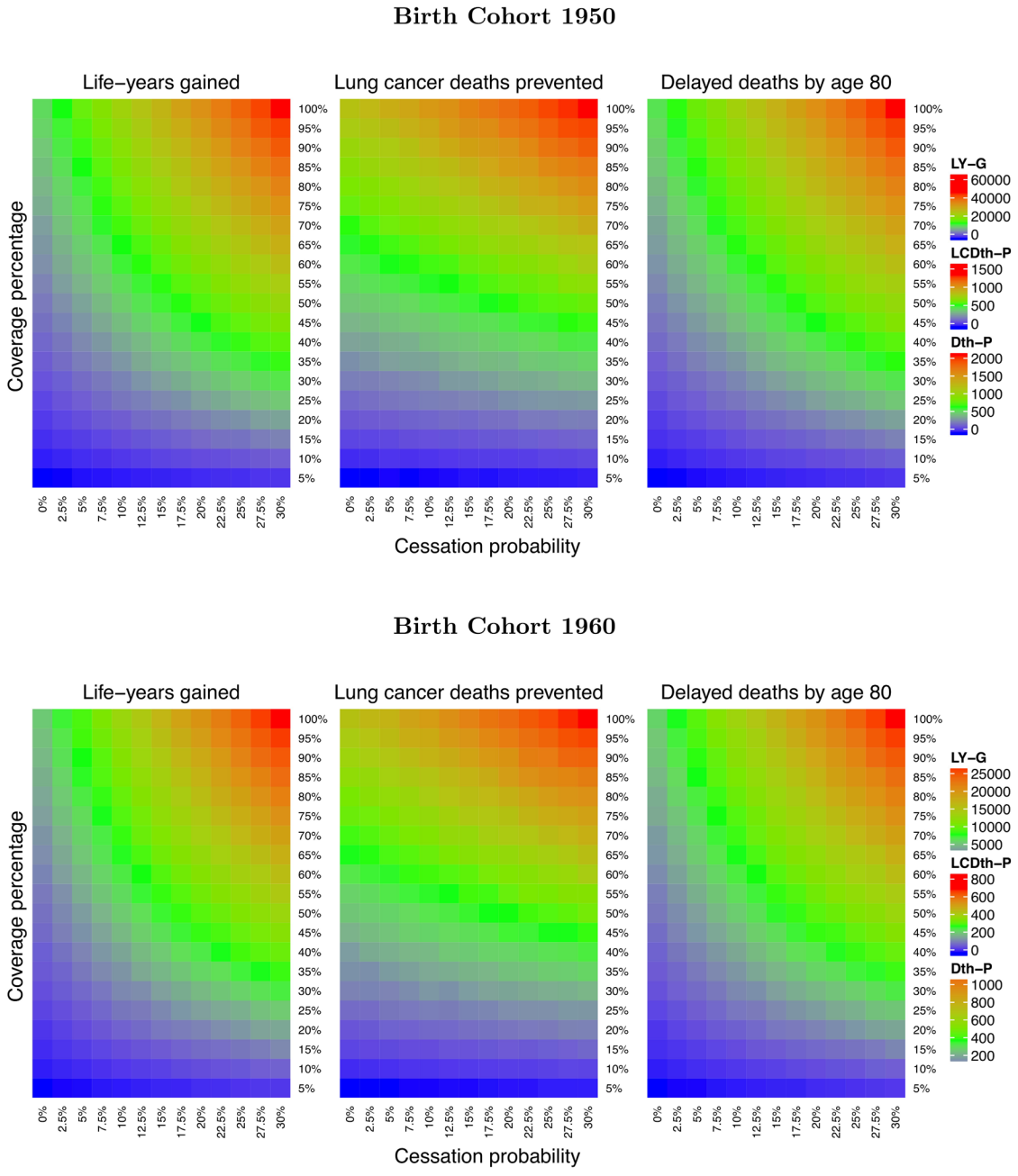


Figure 2.3. Heatmaps of life years gained (left), lung cancer death averted (middle), and deaths delayed by age 80 (right) under different assumptions of screening uptake (5%-100% with 5% increment) and the probability of quitting (0%-30% with 2.5% increment) for birth cohorts 1950 (top panel) and 1960 (bottom panel)



Chapter III

Cost-Effectiveness of Smoking Cessation Interventions in the Lung Cancer Screening Setting: A Simulation Study

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*Cadham and Cao contributed equally to this work.

3.1 Introduction

Lung cancer is the leading cause of cancer death in the United States (US).[71,72] The early detection of lung cancer with low-dose computed tomography is recommended by the US Preventive Services Task Force (USPSTF) based on evidence of lung cancer mortality reductions [10,39] and the Centers for Medicare and Medicaid Services (CMS) includes lung cancer screening as a covered benefit.[9,73]

National guideline groups and CMS also recommend that smoking cessation be provided with lung cancer screening. Data to guide the formal integration of cessation with lung cancer screening are limited,[45] but there are several efforts underway to build the evidence base.[15,57] While past economic analyses suggest lung cancer screening is likely to be cost-effective,[30,40,74,75] the impact of adding cessation to lung cancer screening is less clear.[35,76] None

of the prior economic studies compared different cessation interventions,[22,67,77,78] leaving lung cancer screening programs with limited data to inform their efforts to implement tobacco cessation interventions.

We used an established Cancer Intervention and Surveillance Modeling Network (CISNET) simulation model [3,19,29,30] to estimate the benefits, costs, and cost-effectiveness of delivery of five prototypical types of cessation interventions at the point of lung cancer screening. The results are intended to guide the choice of intervention strategies for smoking cessation programs provided in the lung cancer screening setting.

3.2 Methods

We used the CISNET University of Michigan Lung Cancer Natural History and Screening (MichiganLung) Model for this analysis.[3,19,29,30] The research used deidentified, publicly available data, and was considered human subjects exempt by the University of Michigan and Georgetown University Institutional Review Boards.

3.2.1 Overview

The analysis was conducted from a societal perspective using a lifetime horizon. We modeled one-million men and one-million women screen-eligible from the US 1960 birth cohort, with detailed smoking history simulated from the Smoking History Generator.[3,46,47] USPSTF 2013 criteria[9] were used to define screen eligibility based on the simulated smoking history (age of initiation and cessation and cigarettes/day by age, gender, and cohort. Individuals started screening between ages 55 and 80 at the first age where they had a 30-pack year smoking history and stopped after age 80 or 15 years after smoking cessation, whichever came first. Individuals had an annual probability of developing lung cancer (or not) based on age, gender, and smoking

history.[3,19,29] The model then simulated lung cancer histology, stage and cause-specific survival in the absence of screening.[3,19,29]

3.2.2 Interventions

We compared results of repeat annual screening +/- a smoking cessation intervention at the first screen. The primary analysis assumed the current level of US screening coverage of 15% based on 2017 rates reported in BRFSS;[60] other levels were tested in a sensitivity analysis. Cessation interventions were delivered only at the first screen since there are no data from the screening setting on the effectiveness of repeated interventions among those that fail to quit after the first round. If screening detected cancer, screening modified the time of cancer detection and improved survival compared to that in the absence of screening.

Five categories of smoking cessation interventions were considered based on clinical guidelines, feasibility in screening programs, and data availability: pharmacotherapy alone and pharmacotherapy with either electronic/web-based counseling, telephone counseling (e.g., Quitline referral), group in-person counseling, or individual in-person counseling.[15,45,79] We used a weighted average of the costs and effects of FDA-approved pharmacotherapies including nicotine replacement, bupropion, and varenicline based on their proportions of use (Appendix Table B.1-B.2).[80]

Individuals not exposed to a cessation intervention could quit smoking on their own based on age- and gender-specific background cessation rates.[3,46,47] Smoking cessation for two or more years before the onset of lung cancer resulted in a reduction in the risk of developing lung cancer, lung cancer mortality and other tobacco-related mortality.[19]

3.2.3 Model inputs

The model inputs are summarized in Table 3.1.

3.2.4 Effects

Cancer stage in the absence of screening was based on Surveillance, Epidemiology, and End Results (SEER)-18 data from 2005-2012.[32] Lung cancer-specific survival by age, sex, histology and stage was based on cure models derived from the Cancer Survival Analysis Software.[33]

Lung cancer screening sensitivity was based on calibration to detection rates in National Lung Screening Trial (NLST) and updated to reflect false-positive rates based on the current Lung-RADs classification system.[81]

We calibrated the model predicted lung cancer incidence and mortality rates to the observed data from the NLST CT screening arm for screened individuals and the PLCO control arm for individuals who did not undergo screening.[29] We further calibrated the sex-specific lung cancer mortality for the 1950 and 1960 birth cohorts to the observed US lung cancer mortality data (Appendix Figure B.1 Panel B).

The overall effects of cessation interventions were based on clinical trial data from older adults in the general population,[45,82–88] because data from lung cancer screening settings were limited and did not provide sufficient results by gender or smoking history.[45] The relative risk of stopping (vs. not stopping) smoking after an intervention was applied to the background rate of cessation by age and cohort (Appendix B.1). Competing tobacco- and non-tobacco-related mortality was based on age, sex, and smoking history.[10,52,89]

3.2.5 Utilities

Among those with lung cancer, stage- and phase-of-care-specific utilities were applied to age- and gender-specific general health utilities to determine QALYs (Table 3.1).[30,90–92] We did

not include short-term disutility of screening or undergoing an intervention or the chronic effects of smoking since there are no or limited data to inform these estimates.

Costs

We included the 2019 costs of cessation interventions, screening and follow-up, diagnosis and treatment of lung cancer.[93] Screening costs were based on Medicare reimbursement rates.[30] Cessation intervention costs were estimated using micro-costing of published components of each intervention and supplemented by expert opinion (Appendix B.2). Costs for each component were based on data from the US Bureau of Labor Statistics,[94,95] Red Book,[96] and other nationally-representative data sources.[74,97–100] Age-, stage-, and phase-of-care-specific cancer costs were derived by comparing SEER-Medicare data (2000-2013) for groups of lung cancer patients before and after cancer diagnosis.[101]

3.2.6 Analyses

In primary analyses we compared results of annual screening +/- each cessation intervention, assuming all smokers participate in cessation. Model outcomes included numbers of lung cancer cases and deaths, life-years saved (LYS), quality-adjusted life-years (QALYs), and costs. Each outcome is summarized per 100,000 screen eligible individuals alive at the start of screening at age 55 (smokers and past smokers) and for current smokers only. Costs and effects were discounted by 3% annually.

We first evaluated the added costs and effects of each cessation intervention vs. screening alone. Next, strategies were ranked from least to most costly and incremental costs were divided by incremental QALYs to determine the incremental cost-effectiveness ratio (ICER). The non-dominated strategies were plotted on an efficiency frontier. A strategy was considered efficient if

it increased the slope of the efficiency curve; strategies on the curve after the slope plateaued were considered less efficient.[102]

3.2.7 Sensitivity analyses

We conducted a series of one and two-way sensitivity analyses to test the impact of assumptions and parameter uncertainty on conclusions using the cessation intervention at the inflection point of the efficiency frontier. First, we considered a cohort (1950) with higher smoking rates than the 1960 birth cohort to test the impact of smoking prevalence on results. Next, we varied intervention costs and effects over a range. The lower range of effectiveness was a proxy for population results expected if fewer individuals chose to participate in cessation or those with higher nicotine addiction quit at lower-than-average rates. Two-way analyses modeled results for cessation assuming the best (least expensive and most effective) and worst case (most expensive and least effective). To examine the synergy between cessation and screening, we also varied screening coverage from the base of 15% to 100% holding cessation effects constant. Finally, we modeled an ideal case using the maximum cessation effect, minimum costs, and 100% screening coverage. Probabilistic sensitivity analysis for this CISNET simulation model was not feasible based on the computational capacity of simulating one million men and one million women.[103]

3.2.8 Model validation

The model has been validated in prior analyses.[29,30,52] Here we compared lung cancer rates to observed U.S. mortality and SEER incidence from years 2000-2017 (Appendix Figure B.1).

3.3 Results

The model results were similar to those in our past analyses and estimated comparable age-specific rates of lung cancer incidence and mortality in the absence of screening and cessation as observed in the U.S. from 2000-2017 (Appendix Figure B.2).

3.3.1 Effects of adding cessation to screening

Cessation plus screening resulted in 21-28 fewer lung cancer cases and more LYS and QALYs per 100,000 screen eligible individuals, with only small differences between cessation strategies (Table 3.2). When limiting the population of interest to current smokers, individual counseling and screening (vs. screening only) gained 9,449 QALYs per 100,000 compared to 1,001 QALYs per 100,000 overall screen-eligible population; similar results were seen for other interventions (Table 3.2).

3.3.2 Costs of adding cessation to screening

The discounted costs of screening and lung cancer care were $1.367 billion per 100,000 screen-eligible individuals followed over a lifetime. Cessation interventions increased total costs by 0.32% to 0.75% (Table 3.3).

3.3.3 Cost-effectiveness of adding cessation to screening

When screening plus cessation is compared to screening alone, the added costs for each of the five cessation interventions ranged from $555 to $5,258 per QALY (Table 3.3). Compared incrementally to each other, the ICERs of different cessation interventions plus screening ranged from $555 per QALY to $35,531 per QALY (Table 3.3). Pharmacotherapy alone and group counseling plus pharmacotherapy had higher costs and lower effectiveness and thus were dominated, but both interventions remained close to the efficiency frontier (Figure 3.1).

3.3.4 Sensitivity analyses

The order of the efficiency of the five cessation interventions remained constant across initial sensitivity analyses. In populations with higher smoking prevalence adding cessation to screening was more cost-effective than in the primary analysis, with some cessation interventions considered cost-saving compared to screening alone (not shown). Cessation interventions remained cost-effective even at the lowest rate of assumed effectiveness, and some were cost saving compared to screening alone at the highest effectiveness rate (Appendix Table B.3). Telephone counseling plus pharmacotherapy, one of the interventions at inflection points of the efficiency frontier, was used for additional exemplar sensitivity analyses and results were robust under a range of assumptions (Figure 3.2).

3.4 Discussion

This study provides new knowledge to advance national efforts to incorporate smoking cessation at the point of delivery of lung cancer screening by evaluating the cost-effectiveness of specific smoking cessation interventions. We found that adding cessation interventions to screening (vs. screening alone) would decrease lung cancer cases and deaths and increase life expectancy due to reductions in lung cancer and tobacco-related mortality. There were only small differences between the five classes of cessation strategies evaluated and these interventions increased total lung cancer screening and treatment costs by a modest 0.02% to 0.22%. Most interventions were efficient or close to efficient. The results were robust under a range of assumptions and might even be cost saving under certain circumstances compared to screening alone.

The benefits of cessation in this modeling study are consistent with observational and clinical trial data demonstrating that quitting smoking at older ages reduces cancer incidence and

mortality [104,105] and increases life expectancy, in large part through reductions in death from non-cancer tobacco-related diseases, especially cardiovascular disease.[50,104,106–108]

Previous studies have only considered the cost-effectiveness of screening alone,[30,40,74] or a single generic cessation intervention, and did not compare intervention types.[22,67,77,78] We found that compared to screening alone, all of the cessation interventions that we modeled had benefits and relatively low costs. Our results were consistent with previous studies on the provision of a single modality of cessation with lung cancer screening.[22,67,77,78] However, unlike these previous analyses, our results were not particularly sensitive to cessation intervention characteristics based on their assumed efficacy and cost ranges.

The added costs of providing a cessation intervention to all screen-eligible current smokers under the 2013 USPSTF guidelines were largely offset by future reductions in screening among individuals that are no longer screen-eligible due to cessation and lower cancer treatment costs with fewer lung cancer cases. Further, compared incrementally to each other, the incremental cost-effectiveness ratios of adding different cessation interventions to screening ranged from $555 per QALY to $35,531 per QALY, well below current thresholds of willingness to pay for medical interventions.[109]

The meaningful reductions in the lung cancer deaths and gains in life years saved we observed highlight the importance of offering smoking cessation interventions at the point of lung cancer screening. Despite differences in intervention costs, there were minor differences in cost-effectiveness. These results suggest that the selection of interventions should be based on site-specific factors such as infrastructure and funds available for cessation programs, staff training and availability, onsite workflow, reimbursement levels and individual patient preferences for cessation methods.[15,110] Results from the National Cancer Institute's Smoking

Cessation at Lung Examination (SCALE) Collaboration trials,[15] which include a range of interventions with varying approaches, will provide additional information on feasibility and effects of many of these interventions. In addition, data from community interventions of lung cancer screening will also provide information of screening and cessation outcomes in real-world settings.[57] When these data are available, we will update our model and re-evaluate the uptake and cost-effectiveness of these real-world interventions. Future analyses will also evaluate newer approaches such as text messaging for cessation.[111] Shifts to telehealth are also increasing in cessation settings,[112] may be accelerated by the transformation of the healthcare system in response to COVID-19.[113]

3.4.1 Limitations

This study has several strengths including use of a well-established CISNET model, use of current clinical trial and national data, and extensive sensitivity analyses. However, there are several limitations that should be considered in translating our results to specific settings and populations. First, we modeled guidelines in which were in effect at the time of our study.[9] In March, 2021, the USPSTF published the new lung cancer screening guidelines that reduce the starting age from 55 to 50 and decrease smoking history requirements from 30 pack-years to 20 pack-years.[14] The expanded number of individuals eligible for screening and cessation could potentially result in more favorable cost-effectiveness results since lighter smokers may be more likely to quit than heavier smokers, and younger smokers who quit may gain more life years than older smokers. Inclusion of lighter smokers may also expand screening and cessation access for a more diverse population and could potentially decrease race disparities in lung cancer and other tobacco-related mortality. However, current trials of smoking cessation at the point of screening focus on the current guidelines, thus data on the efficacy of cessation among these on the

expanded eligible population will not be available soon. It will be important to reassess our results in the future and expand sensitivity analyses to include sub-groups defined by smoking habits, race, and other factors under the new guidelines. Since new guidelines may not be in place for some time, our results provide guidance to screening sites looking to implement cessation now under the current guidelines.

A second limit is that while our model inputs were based on the best available literature [7, 40-46],[45,82–88] results could be more (or less) favorable depending on whether adding smoking cessation to screening can achieve economies of scale, if effectiveness varies by level of nicotine addiction or ability to pay out-of-pocket costs associated with cessation, if smokers quit on their own at higher levels than modeled, or if those who quit do not return for future screenings. It is also unclear whether interventions will be more or less effective in the context of a 'teachable moment' at the time of screening,[41] or whether having either a positive or negative screening result will differentially impact the efficacy of cessation interventions [8, 78-81].[15,43,114–116] It will be important to update our model as data become available on any differential effects of negative vs. positive test results on cessation probabilities and whether these vary by type cessation intervention.

Third, to assess efficacy we assumed that all smokers attending lung cancer screening would accept cessation interventions, consistent with prior studies.[74] Limited data exist on cessation use in this setting. While data from the SCALE group will provide some indication of the willingness of smokers to participate in screening and cessation, trial participation rates will likely differ from non-trial rates. Our sensitivity analysis using the lowest intervention effects approximated what would be expected with lower cessation intervention use and indicate that adding cessation to screening maintains benefits under these conditions.

Fourth, we only considered a one-time cessation intervention at the first lung cancer screening exam, given the limited data on the effects of repeated cessation interventions in this setting. If cessation interventions were repeated among those who failed to quit, relapsed, or originally refused, or included a booster to maintain abstinence, the benefits of cessation would likely increase, albeit with added costs.

Finally, we only modeled the costs of lung cancer care and did not include the costs associated with other tobacco-related illnesses. Smoking cessation would lower these costs and would result in even more favorable cost-effectiveness ratios. Additionally, we did not include gains or loss of quality of life associated with smoking status. As data on smoking, screening, and lung cancer therapy evolve, it will be important to model these dynamic factors and their effects on the balance of costs and benefits.

3.5 Conclusion

Providing smoking cessation at the point of lung cancer screening reduces lung cancer cases and deaths and increases life expectancy. All interventions we evaluated provided benefits at reasonable costs.[109] Selection of specific cessation interventions will depend on implementation and dissemination considerations, including the prevalence of smoking in the lung cancer screening eligible population, individual choices of screen eligible smokers, the feasibility of implementation, and local resources.

3.6 Tables and figures

Table 3.1. Model Input Parameters

Parameter	Value/range/description	Source
Smoking Cessation Intervention Relative Risk (95% Confidence Interval)	Methods described in Appendix B.1	Compiled from Cochrane[83–88] and other reviews[45]
Pharmacotherapy Alone	1.93 (1.73-2.15)	
Electronic/Web-Based plus Pharmacotherapy	2.12 (1.90-2.36)	
Telephone Counseling plus Pharmacotherapy	2.20 (1.98-2.44)	
Group Counseling plus Pharmacotherapy	2.14 (1.92-2.38)	
Individual Counseling plus Pharmacotherapy	2.40 (2.15-2.66)	
Screening Follow-up	Follow-up testing, diagnostic procedures, complications and diagnostic mortality	NLST[39]
Screening Procedure Costs, $		Medicare Reimbursement Rates[30,97]
Chest Radiograph	22.32	
LDCT Screening Exams	271.44	
Follow-up Scans	242.28	
Bronchoscopy	361.80	
Mediastinoscopy	324.00	
Needle Biopsy	400.68	
VATS	393.12	
PET/CT	1410.46	
Lung Cancer Treatment Costs	Age, stage, and phase-specific of care treatment costs based on SEER-Medicare data from 2000-2013	Sheehan, et al. 2019[101]
Utility for Cancer-Related States, mean (95% CI)		CISNET Lung Analyses[30]
Stage I NSCLC	0.71 (0.70-0.72)	
Stage II NSCLC	0.68 (0.66-0.70)	
Stage III NSCLC	0.67 (0.66-0.68)	
Stage IV NSCLC	0.66 (0.65-0.67)	
Limited SCLC	0.69(0.68-0.70)	
Extensive SCLC	0.66 (0.65-0.67)	
Terminal SCLC	0.62 (0.54-0.70)	

Smoking Cessation Intervention Costs, mean (range)	Method described in Appendix B.2	Bureau of Labor Statistics, Red Book and other sources[95–100]
Pharmacotherapy Alone	$405 (304-500)	
Electronic/Web-Based plus Pharmacotherapy	$431 (318-539)	
Telephone Counseling plus Pharmacotherapy	$491 (375-603)	
Group Counseling plus Pharmacotherapy	$767 (536-1002)	
Individual Counseling plus Pharmacotherapy	$957 (642-1295)	
NSCLC= non-small cell lung cancer, SCLC= small cell lung cancer, VATS= Video Assisted Thoracic Surgery, PET/CT= positron emission test/computerized tomography		

Table 3.2. Cumulative Lifetime Benefits of Adding Smoking Cessation to Lung Cancer Screening Among Current and Former Smokers Eligible for Lung Cancer Screening vs. Lung Cancer Screening Alone

Intervention	Lung Cancer Cases Averted vs. Screening Alone	Lung Cancer Deaths Averted vs. Screening Alone	Life Years Saved vs. Screening Alone	QALYs Gained vs. Screening Alone	Lung Cancer Cases Averted vs. Screening Alone	Lung Cancer Deaths Averted vs. Screening Alone	Life Years Saved vs. Screening Alone	QALYs Gained vs. Screening Alone
	Per 100,000 Screen Eligible Current and Former Smokers at Age 55[a]				Per 100,000 Screen Eligible Current Smokers at age 55[a]			
Screening + Electronic/Web + Pharmacotherapy	24	15	1,029	820	225	138	9,713	7,741
Screening + Pharmacotherapy	21	13	828	660	200	119	7,816	6,235
Screening + Phone Counseling + Pharmacotherapy	25	15	1,101	877	233	140	10,401	8,285
Screening + Group Counseling + Pharmacotherapy	24	15	1,049	836	225	138	9,907	7,893
Screening + Individual Counseling + Pharmacotherapy	28	17	1,258	1,001	266	158	11,878	9,449

[a] Results are the cumulative total lifetime cancers averted, deaths averted, life-years gained and QALYs gained across the life course for 100,000 simulated individuals. The difference between the results for overall screen-eligible individuals and those for individuals currently smoking reflects the change in the population composition. The proportion of current smokers among screen-eligible varies by age, changing from 75% at age 55 to 45% at age 80. By limiting the population to current smokers at the time of first screen we have removed a large proportion of individuals that are past smokers and would have no effect from the intervention.

Table 3.3. Cost-Effectiveness of Adding Smoking Cessation Interventions to Lung Cancer Screening vs. Screening Alone

Intervention	Total Costs ($)	Total QALYs	$/QALY vs. Screening Alone[a]	Incremental Costs ($)	Incremental QALYs	ICER ($/QALY)
	Per 100,000 Screen-eligible Current and Former Smokers[b]					
Screening, No Cessation	1,366,927,650	2,191,900	-	-	-	-
Screening + Electronic/Web + Pharmacotherapy	1,367,382,397	2,192,720	555	444,284	820	555
Screening + Pharmacotherapy	1,367,585,118	2,192,560	996	Strongly dominated[c]	Strongly dominated[c]	Strongly dominated[c]
Screening + Phone + Pharmacotherapy	1,367,821,002	2,192,778	1,019	438,597	58	7,562
Screening + Group Counseling + Pharmacotherapy	1,370,979,480	2,192,736	4,847	Strongly dominated[c]	Strongly dominated[c]	Strongly dominated[c]
Screening + Individual Counseling + Pharmacotherapy	1,372,191,312	2,192,901	5,258	4,370,236	123	35,531

[a] The added costs per QALY gained for intervention with screening compared to screening alone.
[b] Results are cumulative total lifetime costs and QALYs across the life course for 100,000 screen eligible individuals.
[c] Strategy is considered dominated as it costs more but provides fewer life years or QALYs than the next least costly option. Incremental costs and QALYs for Screening + Pharmacotherapy vs. Screening + Electronic/Web + Pharmacotherapy are $202,717 and -160, respectively. Incremental costs and QALYS for Screening + Group Counseling + Pharmacotherapy vs. Screening + Phone Counseling + Pharmacotherapy are $3,158,425 and -42, respectively. ICERs for the next non-dominated intervention are compared to the next least costly non-dominated intervention.

Figure 3.1. Costs Per Quality Adjusted Life Years Gained from Adding Smoking Cessation Interventions to Lung Cancer Screening

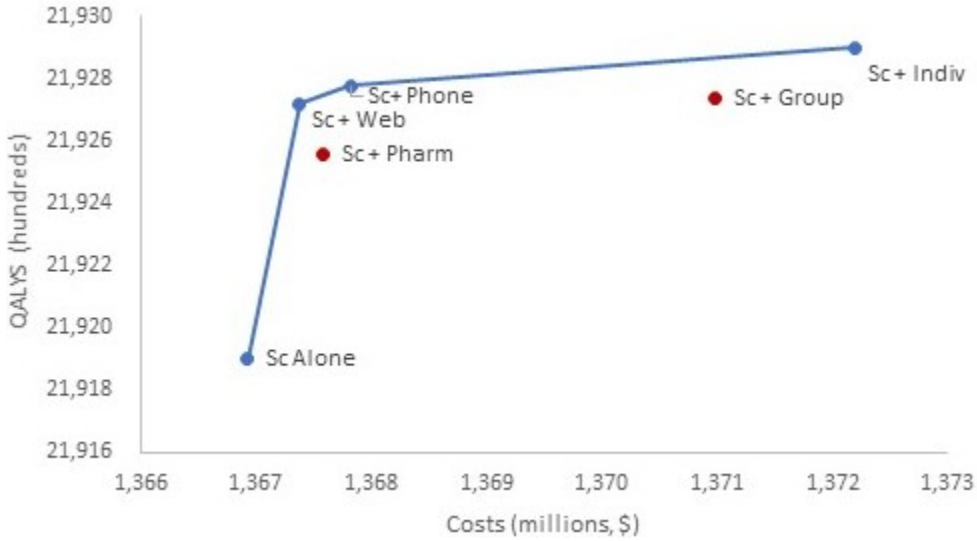


Figure Legend: Strategies are in ascending order of costs: Sc + No Cess - screening plus no cessation; Sc + Pharm - screening plus pharmacotherapy; Sc + Web + Pharm - screening plus electronic/web-based plus pharmacotherapy; Sc + Phone + Pharm - screening plus phone plus pharmacotherapy; Sc + Group + Pharm - screening plus group counseling plus pharmacotherapy; Sc + Indiv + Pharm - and screening plus individual counseling plus pharmacotherapy. Efficient strategies (those in blue that appear along the blue line) were those which yielded an increasing cost to benefit ratio; all other strategies (those in red) are dominated.

Figure 3.2**.** Effects of One-Way and Multi-Way Sensitivity Analyses on Costs per QALY of Screening plus Telephone Counseling and Pharmacotherapy compared to Screening Alone

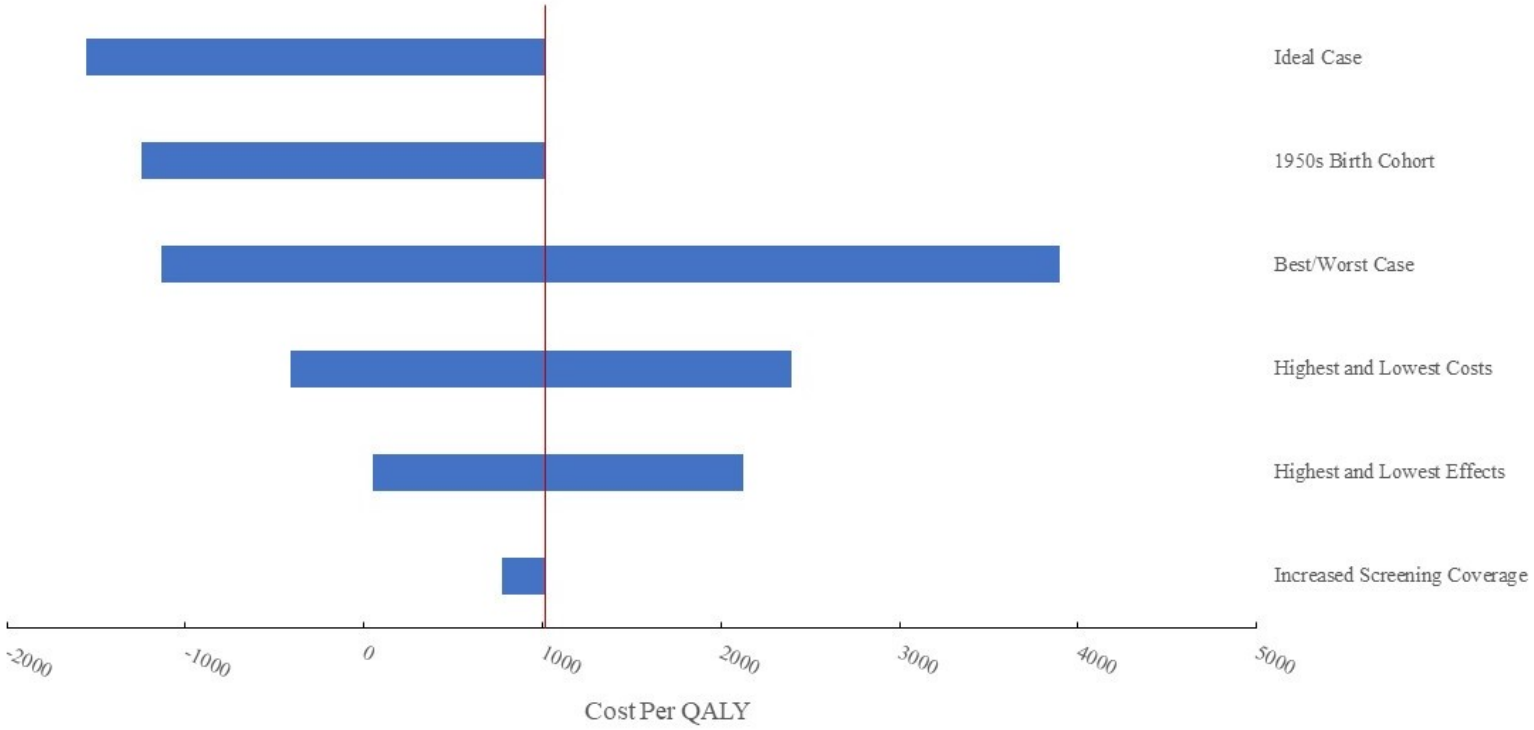


Figure Legend: The vertical red line represented the costs per QALY of the base case screening plus telephone counseling and pharmacotherapy compared to screening alone with screening coverage set to 15% from column 3, Table 3.3 ($1019/QALY). The sensitivity analysis from the top down are: **Ideal case** - Screening plus telephone counseling and pharmacotherapy at the lowest costs ($375) and highest effects (RR = 2.44) compared to screening alone with screening coverage set to 100% in the 1960s birth cohort. **1950s Birth Cohort -** Screening plus telephone counseling and pharmacotherapy among screen eligible individuals in the 1950s birth cohort with base case costs and effects and screening coverage set to 15%. **Best/Worst Case** - Screening plus telephone counseling and pharmacotherapy at the highest costs ($603) and lowest effects (RR= 1.98) compared to screening alone and at the lowest costs ($375) and highest effects (RR= 2.44) compared to screening alone with screening coverage is set to 15% in the 1960s birth cohort. **Increased Screening Coverage** – Screening plus telephone counseling and pharmacotherapy with base case costs and effects and

screening coverage set to 100% in the 1960s birth cohort. **Highest and Lowest Costs** - Screening plus telephone counseling and pharmacotherapy with highest ($603) and lowest costs ($375), base case effects and screening coverage set to 15% in the 1960s birth cohort. **Highest and Lowest Effects -** Screening plus telephone counseling and pharmacotherapy with highest (RR = 2.44) and lowest (RR = 1.98) effects, base case costs and screening coverage set to 15% in the 1960s birth cohort. See also Appendix Table B.5.

Chapter IV

Adaptive Screening for Lung Cancer Using the Threshold Method

4.1 Introduction

Lung cancer continues to be the leading cause of cancer-related mortality in the US, leading to more deaths than the three most common cancers in the US combined (breast, prostate and colon cancer).[1] While US lung cancer mortality is projected to decrease considerably following the ongoing reductions in smoking, lung cancer is still expected to result in over 4 million deaths over the next 50 years.[3] This is due to two main reasons. First, those who have a long history of heavy smoking, whether they quit or not, are at higher lung cancer and lung cancer-related mortality risks versus never smokers. Secondly, lung cancer is an aggressive disease, with a 5-year survival of about 20%.[117] This can be improved to about 60% if lung cancer is diagnosed when it is still localized; however, currently only about 17% of lung cancers are diagnosed at early stages.[117] Thus, in addition to tobacco control efforts, which will result in important reductions in lung cancer in the long-term, early detection and treatment interventions are still needed to further reduce the lung cancer burden in the US in short- and medium-terms.

In 2011, the National Lung Screening Trial (NLST) concluded that three rounds of low-dose computed tomography (LDCT) screening resulted in a 20% reduction in lung cancer mortality compared to chest x-ray screening.[4] In 2013, based largely on the NLST results and supported by Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Working

Group (LWG) decision analyses, the United States Preventive Services Task Force (USPSTF) recommended annual lung cancer screening for ever smokers between the ages of 55 and 80, with at least 30-pack years of smoking history and no more than 15 years since quitting.[9,10] Similarly in 2015, the Center for Medicare and Medicaid Services (CMS) recommended coverage of annual lung cancer screening under Medicare, with the eligibility criteria differing slightly from the USPSTF's (stopping at age 77 instead of 80).[11] Moreover, CMS mandated a counseling and a shared decision-making visit, prior to lung cancer screening (LCS), to discuss the patient's eligibility based on smoking history, the benefits and harms of screening, and the importance of adherence to screening and smoking cessation.[11] In 2021, the USPSTF updated its 2013 recommendations to include younger smokers aged 50 to 54, and those who smoked 20 to 29 pack years.[13]

Even though LDCT screening has proven effective in reducing lung cancer mortality, it is associated with some potential harms, like any other cancer screening intervention. For instance, individuals may have to lose a day of work by attending screening, and experience pre- and post-screen psychological burdens.[118] In addition, the observed false positive rate of LCS in different studies and implementations has ranged from 9 to 50% with a mean of 20%.[119] Under the current management protocols, it is expected to be in the order of 12%.[81,120] In any case, false positive results not only induce further elevated psychological burden,[118] but also lead to unnecessary and potentially invasive follow-up tests, such as biopsies.[4,119] Furthermore, complications or even diagnostic deaths might occur.[4] Hence, when assessing the overall impact from screening, it is necessary to consider both the benefits and the potential harms.

Although USPSTF and CMS both recommend annual screening for an eligible population, earlier studies have suggested that individuals with previous negative screens are at a

considerably lower lung cancer risk.[121,122] According to a modeling study, the risk of lung cancer detection is reduced by 70% following a negative screen, and therefore, lengthening the interval to the next screen and reducing false-positives.[123] Furthermore, given a negative baseline LDCT test result, individualized screening strategies delaying the next screen for a few years can retain 85% of LC mortality reduction at 45% fewer screens compared to screening annually.[124] These findings provide an opportunity to reduce the costs and potential harms of screening without greatly compromising its benefits, by moving low-risk individuals from the recommended annual program to a less intensive dynamic schedule (adaptive scheduling). In this study, we evaluate the impact of such adaptive protocols selected by a "risk threshold method" on screening benefits and harms, considering not only past screening results, but also an individual's smoking history and other risk factors, including sex and age. Furthermore, as life expectancy at the time of screening affects the potential net benefits of lung cancer screening,[23,29] harms from screening may offset the benefits for individuals with limited life expectancy, who may be qualified for a less intensive screening schedule. Therefore, we also consider life expectancy when developing and assessing the performance of screening with adaptive schedules.

4.2 Methods

We developed and implemented a risk threshold method, similar to the threshold method developed by Lee and Zelen for breast cancer screening, to select screening schedules for the whole screen-eligible population, specific groups (by sex or by pack year), and each individual in the study population. We compared the screening-related health outcomes from adaptive screening schedules to those from regular (non-adaptive) schedules (triennial, biennial and annual) using the CISNET Michigan Lung Cancer Smoking and Screening model (MichiganLung).[19,23,29,30] Screening-related health outcomes included lung cancer deaths averted,

life years gained and quality adjusted life years (QALYs) compared with no screening. We further quantified the benefits and harms together using one measure: the discounted QALYs, which is the total QALYs minus the total harms (disutilities) from screening procedures. This research was conducted using publicly available data with deidentified human subject information and thus determined exempt by the University of Michigan Institutional Review Board.

4.2.1 The risk threshold method

The risk threshold method is a deterministic approach that calculates the probability of being in a preclinical disease state conditioned on past negative screens, utilizing a pre-specific risk threshold to determine when to screen.[36] It was originally developed for breast cancer screening by Lee and Zelen, which we now adapt and expand to lung cancer screening. In this method, whenever the probability of an individual to be in preclinical cancer state becomes higher than a pre-specified risk threshold, a screen exam is recommended/given.[36] The threshold method takes three inputs: the age-specific cancer incidence rates, screening sensitivity, and the statistical distribution of preclinical sojourn time.[36] Below is the formula for the probability of being in preclinical state at time *t* after having *r* negative exams at time $t_0, t_1, \dots, t_{r-1}$:

$$P(t|r) = (1-\beta)^r \int_0^{t_0} w(x)Q(t-x)dx$$

$$+ I_{x>0}(r-2) \times \sum_{k=1}^{r-1} (1-\beta)^{r-k} \int_{t_{k-1}}^{t_k} w(x)Q(t-x)dx + \int_{t_k}^{t} w(x)Q(t-x)dx,$$

where β is the test sensitivity, w(t) is the transition rate at time t from normal state to preclinical state, q(t) is the probability density function of the preclinical sojourn time, and $Q(t) = \int_t^{\infty} q(x)dx$. However, w(t) is unobservable, whereas age-specific incidence rate *I(t)* is often

observed and can be obtained from cancer registry data or risk prediction models. We utilize the relationship between *w(t)* and *I(t)* given below to estimate w(t).

$$I(t) = \int_0^t w(x)q(t-x)dx$$

We adapted the threshold method by making the method's inputs specific for lung cancer, accounting also for individual smoking history and resulting lung cancer risk. We did this for different population sub-groups and also on an individualized basis. We used the Two Stage Clonal Expansion (TSCE) dose-response model [31] to obtain individual age-specific lung cancer incidence rates based on the individual's smoking history. We then obtained the average age-specific lung cancer incidence for specific sub-groups of the population. In particular, we conducted separate analyses for the whole screen-eligible population, stratified by sex (males vs females), and stratified by the level of smoking exposure (individuals who had ever smoked 30 to 39 pack years vs those who had smoked more than 40 pack years). We also conducted analyses considering individualized risk to determine individual screening schedules. Screening sensitivity in the threshold method was set to be 0.849 at baseline and 0.786 after baseline according to Lung-RADS.[81] The preclinical sojourn time in the threshold method (how long the cancer remains undetected from onset to clinical diagnosis) was assumed to be exponential distributed and was fitted to individual preclinical sojourn time data simulated from the lung cancer natural history model described below, with rates for the whole population or varied by sex (Appendix Table C.1).

The threshold method was initially developed on a continuous time scale. This can result in unrealistic times between screens (e.g., less than a month), which is clinically infeasible and impractical. Therefore, we adapted the threshold method to result in increments of one year or more between screens. We estimated screening schedules using the threshold method varying the

population subgroup (whole, by sex, by packyear or individualized), the risk threshold, the possible minimum age at start of screening, and with/without adjusting for life expectancy.

We varied the risk threshold from 0.293%, the probability of being in a preclinical state at age 50 for the whole screen eligible population, to 1.01%, the probability of being in preclinical state at age 60 for the whole screen eligible population, with 0.1% increments, resulting in 9 different risk thresholds. We first allow for screening to start any time at or after age 55 according to population or individual risk and constraint by the 2013 USPSTF screening eligibility criteria. We then conducted separate analyses where we fixed the starting age of screening at 55. Subsequently, we incorporated life expectancy into the threshold method by adjusting the age-specific lung cancer incidence by life expectancy at each age. Detailed description of the life expectancy adjustment can be found in the appendix. A summary of the different analyses is given below.

1. Given a lung cancer risk input, obtain the screening schedule based on a pre-specified risk threshold, without fixing the screening starting age at 55. In this case, the starting age generated by the threshold method could be below 55 (the minimum age eligible for screening according the 2013 USPSTF guidelines*). Constrained by the USPSTF eligibility criteria, screening would not occur until the next age in the schedule that is at or over 55*.
2. Given a lung cancer risk input, obtain the screening schedule based on a pre-specified risk threshold, after fixing the screening starting age at 55. In this case, we fix the starting age at 55 and use the threshold method to determine the subsequent ages for screening.
3. Given a lung cancer risk input adjusted for life expectancy, obtain the screening schedule with a pre-specified risk threshold, without fixing the screening starting age at 55.

Constrained by the USPSTF eligibility criteria, screening would not occur until the next age in the schedule that is at or over 55.

4. Given a lung cancer risk input adjusted for life expectancy obtain the screening schedule with a pre-specified risk threshold, fixing the screening starting age at 55.
5. Repeat analyses 1 to 4 for each risk threshold and subgroup combination.

We hereon refer to each scenario using the following acronym: population (whole, bysex, bypky or individual)_life expectancy (adjusted or unadjusted) _starting age (55: fixed or 0: non-fixed)_risk threshold (0.00293 to 0.0101). For example, "individual_unadjusted_55_0.00293" refers to the individualized scenario without adjusting the individual lung cancer risk for life expectancy, fixing the starting age at 55 and with the risk threshold set as 0.00293.

4.2.2 University of Michigan Lung Cancer Natural History and Screening model

To obtain the screening-related health outcomes over the lifetime for different screening schedules, we made use of a previously developed and validated lung cancer natural history and screening model—the UM Lung Cancer Natural History and Screening (MichiganLung) Model—to simulate lung cancer outcomes (onset, histological type, stage progression, clinical detection and mortality or survival), the clinical and survival outcomes of low-dose computed tomography (LDCT) screening.[19,23,29,30] This model takes discrete screening ages as an input, and conducts screening based on screening eligibility and schedule using sensitivities and specificities consistent with the NLST, PLCO trials and the Lung-RADS nodule assessment and management protocols. In this study, we utilized the 2013 USPSTF screening eligibility criteria, being smokers aged 55 to 80 with a smoking history of 30 pack years or more, who have not quit or quit smoking no more than 15 years ago. To reflect clinical guidelines, when the resulting

screening schedules fall outside of screening eligible ages, screening is given only at the scheduled ages within the eligible age range.

The model also simulates detailed follow-up procedures after a positive screen, using probabilities obtained from NLST, including chest radiography, chest CT, PET CT, biopsy, bronchoscopy and other surgical procedures.[125] We quantified the burdens from screening and follow-up tests by multiplying the number of each procedure with its disutility. We further quantify the burdens of follow-up test complications by multiplying the number of each procedure with its corresponding complication rate and disutility. Model parameters description and references were presented in Appendix Table C.2.

4.2.3 Population

We used the CISNET Smoking History Generator (SHG) to generate smoking histories of 1 million men and 1 million women from the 1960 birth cohort, which are meant to be representative of smoking patterns of the current screen-eligible population. The simulated smoking history contained information including smoking starting age, smoking quit age, and the number of daily cigarettes smoked per age, which allows us to determine screening eligibility for each individual. Details of the CISNET SHG have been described elsewhere.[3,46,47]

4.2.4 Utilities and disutilities

We conduct analyses adjusting for the relative changes in quality of life from clinical procedures and lung cancer stages. The age-based quality of life utilities were obtained from a recent cost-effectiveness study of lung cancer screening.[30] The lung cancer-specific utilities varied by sex, age, disease status (with and without lung cancer), lung cancer histology (small cell vs. non-small cell), stage (limited and extended for small cell and I, II, III, IV for non-small cell), and phase (initial, continuous, and terminal).[30] We also quantify the screening burdens

using disutilities—the decrements in quality of life from anxiety and discomfort. The disutilities related to screening and follow-up procedures were derived from published decision analyses.[29]

4.2.5 Non-inferiority schedule

We compare scenarios according to the resulting modeled quality adjusted life years (QALYs) in the corresponding population (or individual). We classify a screening schedule to be non-inferior to the annual screening schedule if the two discounted QALYs are equal.[126] We estimated the lifetime discounted QALYs of different screening schedules using the MichiganLung model. We then compared the discounted QALYs to that of annual screening in search of a non-inferior schedule.

4.2.6 Data envelopment analysis and sensitivity analysis

Efficiency of all scenarios was assessed using data envelopment analysis (DEA), a nonparametric linear programing method for assessing the efficiency of different strategies,[127] with lung cancer deaths averted and life years gained as the two outputs, and the number of screens as the input. A higher score of efficiency indicates higher gains in the outputs given a unit of input. DEA was conducted using the 'dea' function in the 'nonparaeff' package in R (version 4.0.4).[128] This is consistent with the lung cancer screening decision analyses conducted for the USPSTF by the CISNET lung group.[9,10,13,14]

We varied screening-related disutilities by multiplying the baseline values with a factor ranging from 2 to 10 to examine changes in patterns of discounted QALYs.

4.3 Results

Overall, we found that in comparison to standard regular screening recommendations, risk-dependent adaptive screening reduced screening harms while maintaining the same level of

health benefits. The net gains and the balance of benefits and harms from lung cancer screening with efficient adaptive schedules were improved compared to those from regular annual/biennial/triennial screening, especially when the disutilities from screening procedures were more negative.

As the pre-specified risk threshold increased, the starting age selected for screening by the threshold method increased from 50 to 62 years old, and from 55 to 62 if constraint by the USPSTF eligibility criteria (Table 4.1). The interval from the first to the second screen ranged from 1 to 4 years, with a mean of 2.67 years, when the starting age was not fixed. However, when we fixed the starting age to be 55, the interval between the first two screens ranged from 1 to 7 years. Without adjusting for life expectancy, the threshold method resulted in schedules with annual screening after age 70 for all risk thresholds. However, when adjusting for life expectancy, the resulting screening schedules after age 70 were less frequent if the threshold was over 0.5%. Interestingly, some schedules selected by the threshold method turned out to be identical under different assumptions. For example, when considering the whole population without adjusting for life expectancy and with a 0.00293 threshold (whole_unadjusted_55_0.00293) resulted in annual screening from ages 55 to 80. Likewise, when considering men and women separately without adjusting for life expectancy and with a 0.00293 threshold also resulted in annual screening from ages 55 to 80. We consider these duplicated schedules as one in our analyses below, resulting in 138 unique adaptive scheduling scenarios for further analysis.

With regards to risk factors, screening schedules were more frequent for males (vs females), for the 40+ pack year groups (vs 30-39 pack year groups), without adjustment for life expectancy, and with the starting age fixed at age 55 (Table 4.1, Appendix Table C.3-C.4).

Appendix Figure C.1 shows an example of individualized schedules. The figure shows the probability of being in preclinical states given previous negative screens for two individuals in the 1960 birth cohort with distinct smoking history simulated from the SHG. Although these two individuals started smoking both at age 18 and smoked 20 cigarettes per day, the one who quitted earlier (at age 48) had significantly lower risk and thus less frequent screens compared with the one who quitted at age 60.

Figure 4.1 shows the lung cancer deaths averted (LCDs averted) per 100,000 total population by number of LDCT screens per 100,000 total population. The LCDs averted generally increased with the number of screens with diminishing returns. Individualized adaptive schedules (marked as pink circle dots) achieved higher LCDs averted than any other screening schedules with similar numbers of screens. Schedules selected by pack year performed slightly better than schedules selected by sex or for the whole screen-eligible population. Biennial and triennial screenings performed worse than all adaptive screening schedules with similar numbers of screens. In addition, individualized schedules generally had fewer screens than other schedules—the most intensive individualized schedule "individual_unadjusted_55_0.00293" had 193,722 screens per 100,000 population, which was 36,294 fewer screens than annual screening.

Figure 4.2 shows the life years gained (LYG) per 100,000 total population by number of screens per 100,000 total population. LYG per 100,000 total population increased with number of screens in general. Individualized screening schedules had higher LYG than other schedules given a similar number of screens. Biennial and triennial screening performed similarly to those adaptive schedules selected by groups, but worse than individualized schedules.

Table 4.2 shows the screening characteristics and health outcomes for the top 25 scenarios at or near the efficiency frontier, which is the line connecting the scenarios with the

largest benefits (lung cancer deaths and life years gained) for a given the number of screens. Annual screening is the upper anchor of the efficiency frontier (the most intensive schedule, also resulting in the most LCDs averted and LYG). Twenty out of 25 efficient scenarios had individualized screening schedules, and 4 scenarios had adaptive schedules differing by pack year category. The number of false positives per 100,000 population decreased as the number of screens decreased, whereas the number of overdiagnosis per 100,000 population also decreased but at a lower rate. Comparing with no screening, the LCDs averted and LYG per 100,000 total population generally increased with the number of screens. Furthermore, the percent reduction in the number of screens for selected adaptive screening schedules compared with annual screening ranged from 5% to 81%, resulting in 5% to 77% reduction in false positives. The percent reduction in LCDs averted compared with annual screening ranged from 0.5% to 56%, and the percent reduction in LYG ranged from 1% to 59%. For example, the individual_adjusted_0_0.00593 scenario had 60% fewer screens and 57% fewer false positives than annual screening, but its LCDs averted and LYG were only reduced by 32% and 34%, respectively. The number of false-positive screens over LCDs averted, a harm-to-benefit ratio, generally decreased as the number of screens decreased for the top 25 efficient scenarios (Table 4.2).

Figure 4.3 shows the discounted QALYs gained compared with no screening per 100,000 total population by disutility level. After applying baseline disutilities from screening on the lifetime QALYs, annual screening still has the highest discounted QALYs gained (Figure 4.3 (A)). When the disutilities tripled, bypky_unadjusted_55_0.00293 had the highest discounted QALYs gained (Figure 4.3 (B)), whereas if the disutilities increased 5-fold, bypky_adjusted_55_0.00293 had the highest discounted QALYs gained (Figure 4.3 (C)). If the

disutilities increased 10-fold, discounted QALYs gained decreased with the number of screens overall. Individual_adjusted_0_0.00593 and individual_adjusted_55_0.00793 had the highest discounted QALYs gained (Figure 4.3 (D)). Furthermore, schedules controlling for life expectancy had higher discounted QALYs gained than schedules without control on life expectancy, especially when the disutility level was high (Appendix Figure C.2).

Table 4.3 shows the total discounted QALYs for the top 25 scenarios at or near the efficiency frontier. The baseline discounted QALYs increased with the number of screens: annual screening still had the highest lifetime QALYs after discounting for screening burdens. Therefore, we did not identify a non-inferior screening schedule at the baseline disutility level. However, when we increased the baseline disutilities by a factor as low as 2.82, the schedule "bypky_unadjusted_55_0.00293" had as many discounted QALYs as the annual screening. Efficient screening schedules with fewer screens were preferable when the disutilities were high. For example, the schedule "individual_adjusted_0_0.00593" had the highest discounted QALYs when the disutilities increased by 10 times.

4.4 Discussion

In this study, we applied a risk threshold method to select adaptive screening schedules for different screen-eligible populations (e.g., males and females and groups with different smoking histories) under varying risk thresholds, fixing/non-fixing the minimum starting age and with/without life expectancy adjustments. We utilized an established lung cancer screening microsimulation model to compare the long-term health benefits and harms from screening with adaptive screening schedules with those from screening with regular (non-adaptive) annual, biennial, and triennial schedules. We found that annual screening—the most intensive strategy—was the upper anchor in all efficiency frontiers, indicating that this scenario had the highest

health benefits and the highest number of screens. However, the percentage reduction in health gains (LCDs averted and LYG) in adaptive screening strategies versus annual screening was much lower than the percentage decrease in the number of screens and false positives, indicating improvements in efficiency and a better harm-to-benefit ratios from adaptive screening.

Most efficient scenarios (those on the efficiency frontiers for both LCDs averted and LYG) were individualized screening schedules, i.e., strategies where the screening schedule varies by individual according to their own sex and smoking history. Individualized schedules also had fewer screens than annual screening, with only 10% of individuals receiving annual screening in the most intensive individualized scenario. This result suggests that annual screening is not necessary for all screen-eligible individuals, and the decision on the screening interval should vary according to each person's individual risk and smoking history. In addition, strategies where the schedule varied according to pack-year level (by-pack-year strategies) resulted in more benefits for the same level of screening than adaptive schedules varying only by sex or identical for the whole population. Different pack year groups (30-39 vs 40 or more pack years) had different lung cancer risks, leading to distinct and potentially more suitable schedules for each group when considered separately. On the other hand, males' and females' lung cancer risks may not be sufficiently different to justify different schedules. This finding indicates that identifying groups with distinct enough lung cancer risks in the screen-eligible population may lead to more optimal screening schedules by group, and therefore result in better health gains given limited resources.

Patients' preferences towards screening may greatly impact the potential benefits from screening. The patterns of discounted QALYs by the number of screens varied widely by the level of disutilities, and annual screening no longer had the highest benefits if the disutilities

were medium to high (around 3 times or higher than baseline). This observation indicates that when patients' perceived burdens on screening and related procedures were medium to high, less intensive schedules, such as the individual_adjusted_0_0.00593 scenario, may be preferable to one-size-fits all approaches. Other studies have also found that a patient's preference towards screening may significantly affect the potential benefits from screening, and thus a shared decision-making session prior to screening is needed to better understand the patient's attitudes.[29,129,130] A discussion of an alternative, less intensive screening schedule calculated on the fly by the threshold method, could be provided during the shared decision-making session as well.

Studies for other cancer sites have explored the possibility of implementing different screening intervals for groups with different cancer risks. Lower risk groups could potentially receive less intensive screening and higher risk groups receive standard or more intensive screening. For example, biennial screening mammography is currently recommended for women aged 50 to 74 in the United States.[131] However, a recent modeling study suggests that average-risk women with low breast density undergoing triennial screening and high-risk women with high breast density undergoing annual screening could have a better balance of benefits and harms than every woman going through biennial screening.[132] In addition, some countries have started to implement learning screening programs, in which individuals are invited to be randomized into groups with different screening characteristics, e.g., various screening intervals for different groups.[133] For instance, the Norwegian cervical cancer screening program is inviting women to join the two screening arms: HPV testing plus pap smear every 5 years and pap smear alone every 3 years.[133] Kalager and Bretthauer further proposed an even longer screening interval—10 to 15 years for those that are HPV-vaccinated.[133] Furthermore, the European Union

is conducting a multi-country clinical trial (4-IN-THE-LUNG-RUN) to study the effectiveness and cost-effectiveness of the risk-based less intensive lung cancer screening after a negative CT screen.[134]

This study has several strengths. While we await the results from clinical trials and observational studies, we have applied a modeling framework to simulate and project the potential impact of implementing lung cancer risk-oriented screening intervals on short- and long-term benefits and harms from screening. We adapted a risk threshold method, previously developed for breast cancer screening, to obtain lung cancer screening schedules given lung cancer risks, preclinical sojourn time distribution and screening sensitivity. The threshold method is a deterministic model, which is straightforward and timesaving as it does not require any simulation. Its input parameters can be obtained via surveillance data, published risk models or literature reviews. Instead of randomly selecting screening ages, the threshold method provides a solid analytical foundation that guides the decision of when to screen. We then used a well-established CISNET lung cancer natural history and screening simulation model to compare the effectiveness of strategies with adaptive and regular (non-adaptive) schedules. This model is able to reproduce the lung cancer mortality observed in the US population and the short-term outcomes of three rounds of LDCT screening in randomized control trials by arm, lung cancer histology, and stage.[18,28] The model has been previously used to study the long-term benefits and harms of various lung cancer screening eligibility criteria,[13] the cost-effectiveness of strategies varying the age at stopping screening,[30] and the effectiveness of risk-based screening strategies for the US population.[23] Finally, we used a validated model of individual smoking histories in the US that has been shown to reproduce the history of smoking by birth-cohort for the US population.[19–21]

Despite the number of strengths, our study also has a few caveats. First, the risk threshold method may be sensitive to the assumed sojourn time distribution and parameter values. For example, if we set the preclinical sojourn time (PST) distribution to be Weibull-distributed with previously published shape and scale parameters, some of the transition rates output from the threshold method may become negative. However, the threshold method is more robust to an exponentially distributed PST, and therefore, we re-fitted the PST (one of the natural history components from the MichiganLung model) using an exponential distribution. It is unclear how the selection of a different PST distribution may affect the schedules selected by the threshold method, so further methodological studies are needed in this area.

Secondly, the threshold method treats each negative screen as an independent event. However, individuals with a negative screen may be more likely to be tested negative in the subsequent screens (interaction), and thereon at an even lower risk of lung cancer. Hence, we could incorporate an additional term in the formula of probability being in preclinical state to further deflate the probability if the individual has more than one negative screen. One potential option of this term is $e^{-\rho(r-k)}$, where $\rho > 0$, $e^{-\rho}$ is the hazard ratio of lung cancer risk with one additional negative screen, and could be potentially obtained from the literature. The new formula is given as below:

$$P(t|r) = (1-\beta)^r \int_0^{t_0} w(x)Q(t-x)dx$$
$$+ I_{x>0}(r-2) \times \sum_{k=1}^{r-1} e^{-\rho(r-k)} \times (1-\beta)^{r-k} \int_{t_{k-1}}^{t_k} w(x)Q(t-x)dx) + \int_{t_k}^{t} w(x)Q(t-x)dx,$$

Thirdly, we used the risk estimates from the Two-Stage Clonal Expansion model as the input to the threshold method. However, other well-validated lung cancer risk models are also used in academic and clinical settings, including the Bach model,[135] the LCRAT model,[136] and

the PLCOm2012 model.[137] In future work we will assess the impact of using different underlying lung cancer risk models on the resulting screening schedules. Third, the threshold method is unable to inform how to classify groups for receiving less or more intensive screening. Instead, we pre-selected the population sub-groups (males vs. females and 30-39 pack years vs. 40+ pack years) based on expert opinions, and then conducted the performance for each sub-group. Other methods that jointly determine optimal schedules and evaluate their performance simultaneously, such as those from Partially Observed Markov Decision Processes may be preferable, but could also be more computationally intensive.[138,139] Finally, in this study, we only considered 100% screening adherence rate. Each screen-eligible individual will adhere to lung cancer screening at the assigned schedule. However, recent studies found that the adherence rate to annual lung cancer screening varies widely from 12% to 91%, depending on smoking status, age, education, and race.[140] For example, older individuals aged 65 to 73 are more likely to adhere than younger individuals aged 50 to 64.[140] If younger individuals are more compliant with less intensive screening than annual screening, the adaptive schedules selected by the threshold method will be preferable. However, it is also possible that those who are less likely to adhere skip irrespectively of the schedule. In this case, the potential benefits of all scenarios considered in our study will be reduced, but the relative performance between scenarios could remain the same. Future studies are needed to understand how adherence plays the role.

In summary, our findings illustrate that lung cancer risk-oriented adaptive schedules can provide a better balance of screening benefits and harms than the currently implemented annual screening. Our study provides a possible solution to optimize lung cancer screening, by reducing lung cancer screening burdens while preserving the majority of its benefits. Both individual lung cancer risk and individual preferences play an important role in the potential net gain from lung

cancer screening, which suggest calls for a patient-centered decision-making process and tailored screening intervals.

4.5 Tables and figures

Table 4.1. Screening schedules selected by the threshold method by risk threshold for the whole screen-eligible population (36 scenarios)

Scenario	Schedule
Unadjusted_0_0.00293	50, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.00293	50, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Unadjusted_0_0.00393	52, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.00393	52, 55, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Unadjusted_0_0.00493	54, 57, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.00493	54, 57, 59, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Unadjusted_0_0.00593	56, 58, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.00593	56, 59, 61, 63, 65, 66, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 80
Unadjusted_0_0.00693	57, 60, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.00693	57, 61, 63, 65, 67, 68, 70, 71, 73, 74, 76, 77, 79, 80
Unadjusted_0_0.00793	58, 61, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.00793	59, 62, 65, 67, 69, 71, 72, 74, 76, 78, 79
Unadjusted_0_0.00893	59, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81
Adjusted_0_0.00893	60, 64, 66, 69, 71, 73, 75, 77, 79
Unadjusted_0_0.00993	60, 63, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.00993	62, 65, 68, 71, 73, 76, 78
Unadjusted_0_0.0101	60, 63, 65, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_0_0.0101	62, 66, 68, 71, 73, 76, 78
Unadjusted_55_0.00293	55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_55_0.00293	55, 56, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Unadjusted_55_0.00393	55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_55_0.00393	55, 57, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Unadjusted_55_0.00493	55, 57, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80

Adjusted_55_0.00493	55, 58, 60, 61, 63, 64, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Unadjusted_55_0.00593	55, 58, 60, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_55_0.00593	55, 58, 61, 63, 64, 66, 67, 69, 70, 71, 72, 73, 75, 76, 77, 78, 80
Unadjusted_55_0.00693	55, 59, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_55_0.00693	55, 59, 62, 64, 66, 68, 69, 71, 72, 74, 75, 76, 78, 80
Unadjusted_55_0.00793	55, 59, 62, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_55_0.00793	55, 60, 63, 66, 68, 70, 71, 73, 75, 76, 78, 80
Unadjusted_55_0.00893	55, 60, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_55_0.00893	55, 61, 65, 67, 69, 71, 73, 75, 78, 80, 82
Unadjusted_55_0.00993	55, 61, 63, 65, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81
Adjusted_55_0.00993	55, 62, 66, 69, 71, 74, 76, 78
Unadjusted_55_0.0101	55, 61, 64, 65, 67, 68, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
Adjusted_55_0.0101	55, 62, 66, 69, 71, 74, 76

Table 4.2. Benefits and harms of the top 25 scenarios at or near the efficient frontier for the 1960 US birth cohort

Scenario	Number of screens%	Number of false positives %	Number of over-diagnosis%	Lung Cancer Death averted compared with no screening %	Life Years Gained compared with no screening %	False positives per LCD averted	Percent reduction in screens vs. annual screening	Percent reduction in false positives vs. annual screening	Percent reduction in LCD averted vs. annual screening	Percent reduction in LYG vs. annual screening
Annual*	230,016	12,684	59	401	5,729	32	NA	NA	NA	NA
bypky_unadjusted_55_0.00293	217,940	12,067	58	399	5,655	30	5%	5%	0%	1%
bypky_adjusted_55_0.00293	207,168	11,572	56	382	5,546	30	10%	9%	5%	3%
individual_unadjusted_55_0.00293	193,722	10,901	57	388	5,458	28	16%	14%	3%	5%
bypky_adjusted_55_0.00393	188,708	10,677	56	377	5,341	28	18%	16%	6%	7%
individual_unadjusted_0_0.00293	188,002	10,587	57	379	5,375	28	18%	17%	5%	6%
individual_unadjusted_0_0.00393	170,398	9,673	56	367	5,048	26	26%	24%	8%	12%
individual_adjusted_55_0.00293	163,081	9,365	54	357	5,033	26	29%	26%	11%	12%
bypky_unadjusted_55_0.00693	160,828	9,283	55	360	4,859	26	30%	27%	10%	15%
individual_unadjusted_55_0.00593	146,175	8,513	55	351	4,786	24	36%	33%	12%	16%
individual_unadjusted_0_0.00593	140,240	8,068	53	344	4,619	23	39%	36%	14%	19%
individual_adjusted_55_0.00393	136,923	8,008	51	333	4,702	24	40%	37%	17%	18%
individual_adjusted_0_0.00393	129,374	7,536	51	324	4,506	23	44%	41%	19%	21%
individual_unadjusted_55_0.00793	124,747	7,405	52	327	4,365	23	46%	42%	18%	24%
individual_unadjusted_55_0.00893	115,284	6,894	53	320	4,211	22	50%	46%	20%	26%

individual_unadjusted_0_0.00793	115,248	6,694	51	321	4,149	21	50%	47%	20%	28%
individual_unadjusted_0_0.00993	96,799	5,658	51	292	3,739	19	58%	55%	27%	35%
individual_unadjusted_0_0.0101	95,893	5,608	51	294	3,715	19	58%	56%	27%	35%
individual_adjusted_0_0.00593	91,226	5,456	46	274	3,765	20	60%	57%	32%	34%
individual_adjusted_55_0.00693	85,115	5,368	44	255	3,554	21	63%	58%	36%	38%
individual_adjusted_0_0.00693	76,053	4,679	44	248	3,339	19	67%	63%	38%	42%
individual_adjusted_0_0.00793	63,401	4,036	40	223	3,031	18	72%	68%	44%	47%
individual_adjusted_0_0.00893	53,235	3,466	37	205	2,739	17	77%	73%	49%	52%
individual_adjusted_0_0.00993	44,934	3,028	34	185	2,427	16	80%	76%	54%	58%
individual_adjusted_0_0.0101	43,918	2,961	32	175	2,328	17	81%	77%	56%	59%
% Number per 100,000 total population *** whole_unadjusted_55_0.00293 and Bysex_unadjusted_55_0.00293 have the same screening schedule as annual screening**										

Table 4.3. Discounted QALYs by the disutility level of the top 25 scenarios at or near the efficient frontier for the 1960 US birth cohort

Scenario	Number of screens	Total QALYs	Total disutilities	Discounted QALYs – baseline	Discounted QALYs – 2.82 times	Discounted QALYs – 5 times	Discounted QALYs – 10 times	Disutility factor *
NoScreen	0	3,082,764	0	3,082,764	3,082,764	3,082,764	3,082,764	NA
Annual	230,016	3,087,182	434	3,086,748	3,085,957	3,085,014	3,082,846	NA
bypky_unadjusted_55_0.00293	217,940	3,087,138	418	3,086,720	3,085,957	3,085,048	3,082,958	2.82
bypky_adjusted_55_0.00293	207,168	3,087,067	403	3,086,664	3,085,929	3,085,053	3,083,040	3.73
individual_unadjusted_55_0.00293	193,722	3,086,981	388	3,086,593	3,085,884	3,085,040	3,083,099	4.43
bypky_adjusted_55_0.00393	188,708	3,086,884	378	3,086,506	3,085,816	3,084,993	3,083,103	5.38
individual_unadjusted_0_0.00293	188,002	3,086,911	379	3,086,532	3,085,841	3,085,017	3,083,122	4.96
individual_unadjusted_0_0.00393	170,398	3,086,639	355	3,086,284	3,085,637	3,084,864	3,083,090	6.90
individual_adjusted_55_0.00293	163,081	3,086,659	343	3,086,316	3,085,689	3,084,942	3,083,225	5.80
bypky_unadjusted_55_0.00693	160,828	3,086,494	342	3,086,152	3,085,529	3,084,786	3,083,079	7.48
individual_unadjusted_55_0.00593	146,175	3,086,429	322	3,086,107	3,085,520	3,084,820	3,083,211	6.74
individual_unadjusted_0_0.00593	140,240	3,086,302	311	3,085,991	3,085,423	3,084,746	3,083,189	7.20
individual_adjusted_55_0.00393	136,923	3,086,380	303	3,086,077	3,085,524	3,084,865	3,083,350	6.14
individual_adjusted_0_0.00393	129,374	3,086,241	292	3,085,949	3,085,417	3,084,783	3,083,325	6.63
individual_unadjusted_55_0.00793	124,747	3,086,092	288	3,085,804	3,085,279	3,084,652	3,083,213	7.48
individual_unadjusted_55_0.00893	115,284	3,085,973	273	3,085,700	3,085,202	3,084,609	3,083,245	7.52
individual_unadjusted_0_0.00793	115,248	3,085,928	274	3,085,654	3,085,155	3,084,559	3,083,190	7.85
individual_unadjusted_0_0.00993	96,799	3,085,601	243	3,085,358	3,084,915	3,084,387	3,083,173	8.29
individual_unadjusted_0_0.0101	95,893	3,085,588	241	3,085,347	3,084,907	3,084,382	3,083,176	8.29
individual_adjusted_0_0.00593	91,226	3,085,637	227	3,085,410	3,084,995	3,084,500	3,083,363	7.49
individual_adjusted_55_0.00693	85,115	3,085,501	215	3,085,286	3,084,895	3,084,428	3,083,355	7.68
individual_adjusted_0_0.00693	76,053	3,085,305	199	3,085,106	3,084,742	3,084,309	3,083,313	8.01
individual_adjusted_0_0.00793	63,401	3,085,077	174	3,084,903	3,084,585	3,084,205	3,083,334	8.12
individual_adjusted_0_0.00893	53,235	3,084,858	153	3,084,705	3,084,426	3,084,093	3,083,327	8.29

individual_adjusted_0_0.00993	44,934	3,084,612	135	3,084,477	3,084,232	3,083,939	3,083,267	8.59
individual_adjusted_0_0.0101	43,918	3,084,531	131	3,084,400	3,084,160	3,083,875	3,083,219	8.77

*$Disutility\ factor = \frac{QALYs(annual) - QALYs(adaptive\ schedule)}{Disutilities(annual) - Disutilities(adaptive\ schedule)}$; a factor that needs to be multiplied with the baseline disutilities such that the discounted QALYs of a certain adaptive screening schedule is equal to that of the annual screening

Yellow shading: highest discounted QALYs

Green shading: lowest discounted QALYs among screening scenarios or disutility factor

Figure 4.1. Lung cancer deaths averted compared with no screening for the 138 adaptive and 3 regular screening scenarios for the 1960 US birth cohort. The gray curve is the efficiency frontier, connecting the dots with the highest lung cancer deaths averted given numbers of screens. Yellow dots represent regular screening: annual (circle), biennial (square), and triennial (triangle). Individualized schedules were highlighted in pink circle, by-pack-year schedules were colored in dark blue, by-sex schedules were colored in light green, while the schedules selected for the whole screen-eligible 1960 birth cohort were colored in light blue

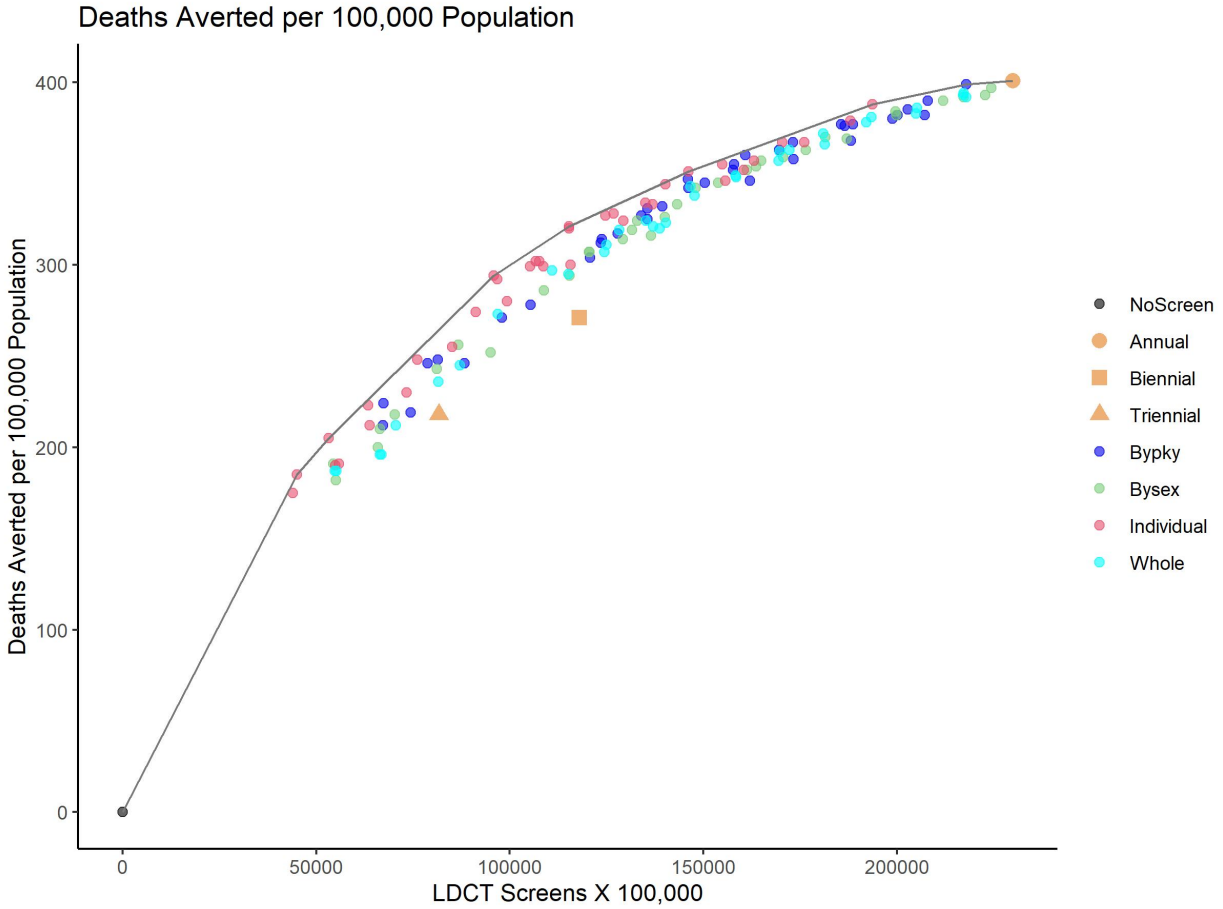


Figure 4.2. Life years gained compared with no screening for the 138 adaptive and 3 regular screening scenarios for the 1960 US birth cohort. The gray curve is the efficiency frontier, connecting the dots with the highest life years gained given numbers of screens. Yellow dots represent regular screening: annual (circle), biennial (square), and triennial (triangle). Individualized schedules were highlighted in pink circle, by-pack-year schedules were colored in dark blue, by-sex schedules were colored in light green, while the schedules selected for the whole screen-eligible 1960 birth cohort were colored in light blue

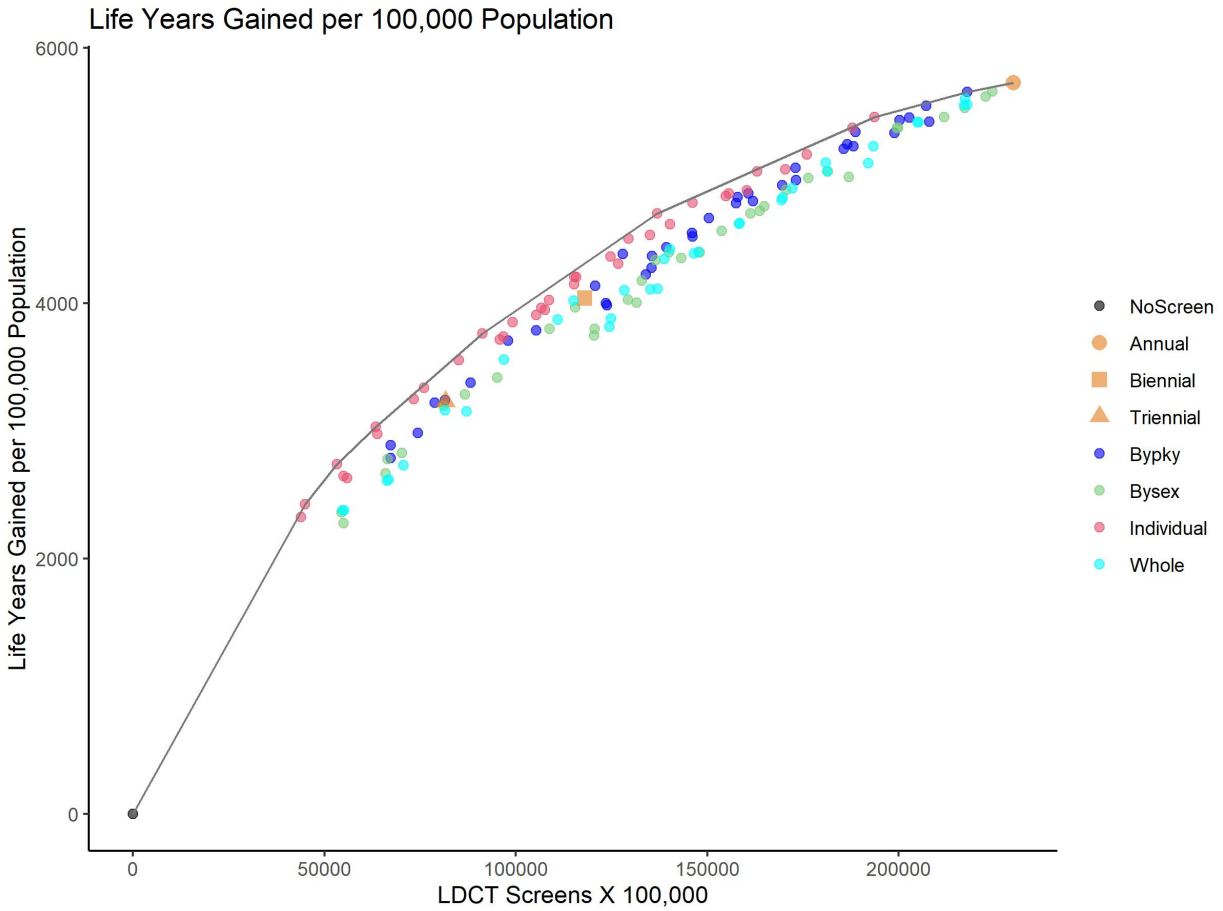
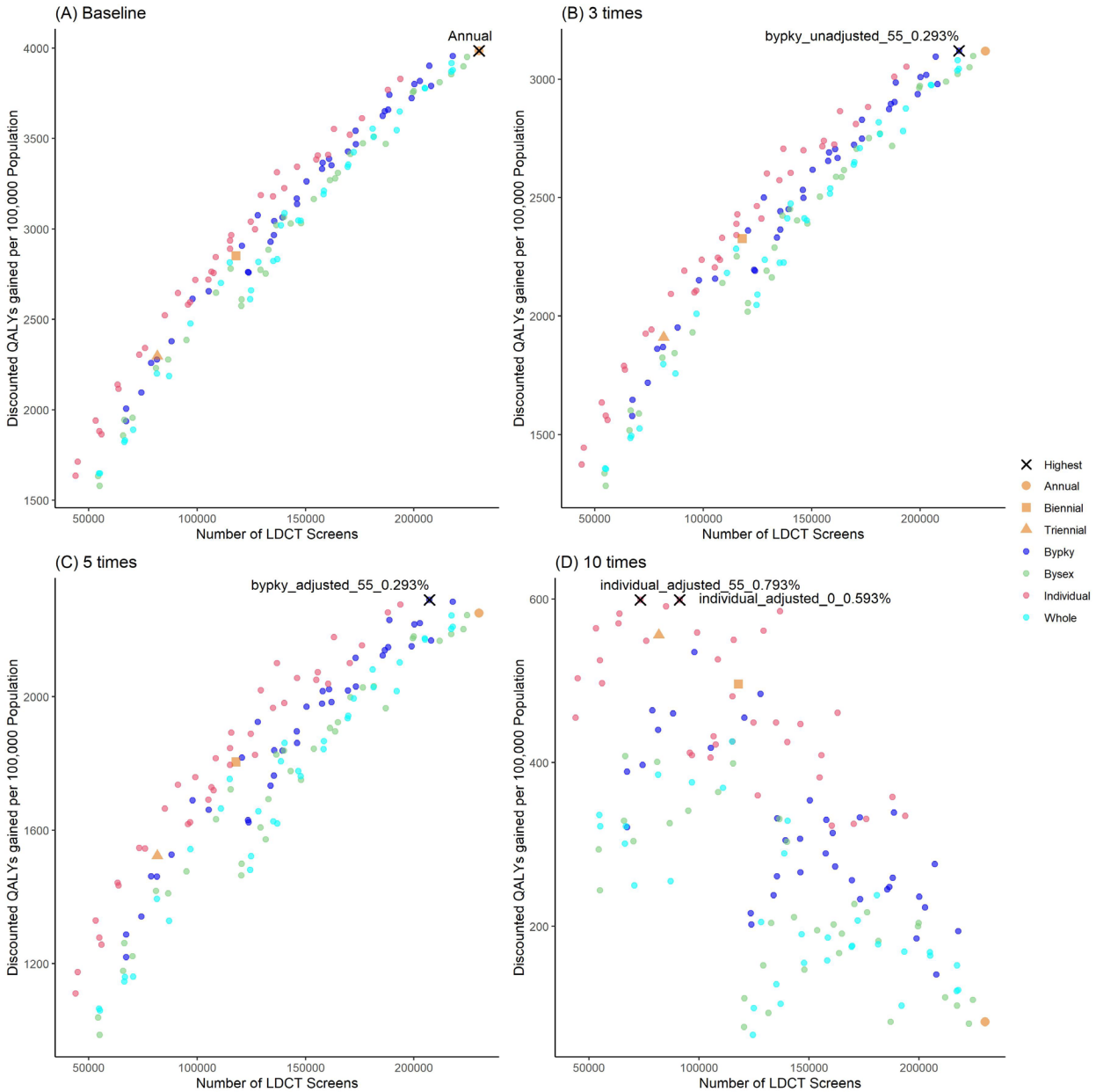


Figure 4.3. Total discounted QALYs gained compared with no screening by the disutility level for the 138 adaptive and 3 regular screening scenarios for the 1960 US birth cohort. (A) Baseline disutilities; (B) 3-times disutilities; (C) 5-times disutilities; and (D) 10-times disutilities. Yellow dots represent regular screening: annual (circle), biennial (square), and triennial (triangle). Individualized schedules were highlighted in pink circle, by-pack-year schedules were colored in dark blue, by-sex schedules were colored in light green, while the schedules selected for the whole screen-eligible 1960 birth cohort were colored in light blue. Black crosses highlighted the scenario(s) with the highest discounted QALYs, being (A) annual screening, (B) bypky_unadjusted_55_0.00293, (C) bypky_adjusted_55_0.00293, and (D) individual_adjusted_55_0.00793 and individual_adjusted_0_0.00593



Chapter V

Cost-Effectiveness of Adaptive Schedules Identified by the Threshold Method

5.1 Background

In Chapter IV, we found that adaptive schedules selected by the threshold method had comparable effectiveness as the current recommendation of annual screening, and could provide better benefit vs harm trade-offs. Besides clinical effectiveness, it is also important to understand the economic efficiency of the adaptive schedules, as national cancer care costs have been projected to increase from $185 billion in 2015 to $245 billion in 2030, and lung cancer is one of the costliest cancers in the United States.[141,142]

We observed a lower screening intensity, false-positive rates, and overdiagnosis rates when screening using adaptive versus regular (non-adaptive) schedules in Chapter IV (Table 5.1). Thus, screening-related costs and overdiagnosis treatment costs should be lower for the adaptive schedules. However, treatment costs could be higher for adaptive schedules compared with annual screening due to a reduction in screening efficacy potentially resulting in higher numbers of advanced stage cancers, which require more costly treatments.[101] On the other hand, since the timing of screening is identified based on the risk of being in the preclinical state given prior exams, the screening efficacy and thus health benefits measured using quality adjusted life years (QALYs), a critical component to determine the cost-effectiveness of an intervention, should not be affected significantly. Therefore, in this chapter, we conduct a cost-effectiveness

analysis of adaptive schedules relative to annual screening to determine the net economic costs and health benefits of the adaptive strategies identified in Chapter IV.

5.2 Methods

This study estimated costs, effectiveness, and cost-effectiveness from the health care sector perspective. We considered the same 138 adaptive schedules as in Chapter IV, and 3 regular (non-adaptive) screening schedules: triennial, biennial and annual. We utilized the same microsimulation model—the MichiganLung model as in Chapter IV to generate individual life history (age at death), natural history of lung cancer (age at diagnosis, histology, stage, and lung cancer-specific mortality), and screening outcomes (screening results, follow-up procedures, complications, and diagnostic death), given individual's smoking history obtained from the CISNET Smoking History Generator (SHG).[46,47]

5.2.1 Study population

We used the same study population as Chapter IV, which was 1 million men and 1 million women from the 1960 birth cohort simulated using the SHG.

5.2.2 Costs and health utilities

The MichiganLung model had the following screening and diagnostic procedures incorporated, including screening low-dose computed tomography (LDCT), follow-up LDCT scan, bronchoscopy, mediastinoscopy, needle biopsy, and positron emission tomography/CT. Costs related to screening and diagnostic procedures and lung cancer treatment were obtained from previous studies, and all costs were inflated to 2020 US dollars with an assumed 3% annual inflation rate.[20,30,101,143] Procedure costs were invariant by age, whereas treatment costs differed by age, histology, stage and phase of care—initial phase (the initial 6 months from cancer

diagnosis), continuous phase, and terminal phase (the last 6 months in life).[20,30,101,143] We assumed that all costs incurred before age 55 were the same as costs at age 55, and costs incurred after age 85 were the same as costs at age 85.

The age-based quality of life utilities and lung cancer-specific utilities were the same as Chapter IV. We discounted costs, life years and QALYs at an annual rate of 3%.

5.2.3 Outcome measures

We determined the dominance of each strategy and classify it into one of the three categories: dominated, weakly dominated and dominant (non-dominated). A strategy is dominated when it has higher costs but lower or equal benefits than at least one other strategy. If a strategy has higher costs and lower benefits than those from a combination of two other strategies, the strategy is weakly or extendedly dominated. After ruling out the dominated and weakly dominated strategies, we obtain the dominant (non-dominated) strategies.

We calculated costs per life year gained or QALY gained compared with no screening for all scenarios. We then calculated the incremental cost-effectiveness ratio (ICER), defined as the incremental cost divided by the incremental life years gained or QALYs gained, for each non-dominated screening strategy compared with previous non-dominated scenarios sorted in the ascending order of total costs.

Per US standard protocol, we considered ICERs falling below a societal willingness-to-pay (WTP) threshold of $100,000 per QALY as cost-effective.[144] The most cost-effectiveness strategy is the one with ICER per QALY under and closest to $100,000.[145]

5.2.4 Sensitivity analysis

We conducted one-way sensitivity analysis by varying 1) the screening costs, 2) the continuous phase costs for stage I non-small cell lung cancer (NSCLC), and 3) the terminal phase costs for stage IV NSCLC by 15% around the base-case values, as these are the top 3 largest components of the total costs.

We conducted probabilistic sensitivity analyses by varying all the costs and health utilities under assigned distributions. We varied the costs by 15% around the base-case values. We obtained the base-case values and variances of the health utilities from a previously published analysis,[30] and assumed beta distributions for all utilities. We sampled the value of costs and utilities and re-evaluated the dominance and ICERs for all scenarios in 100,000 iterations. We considered a range of WTP threshold from $0 to $200,000 with $1,000 increment and determined the probability of each scenario being cost-effective at a specific threshold. We then plotted the probability of being cost effective by the WTP threshold, i.e., the cost-effectiveness acceptability curve, for the 9 dominant strategies at base case.

5.3 Results

Figure 5.1 and Appendix Figure D.1 show the relationship between the total QALYs gained compared with no screening, total costs and total number of screens for all 141 scenarios considered. Total costs generally increased with number of screens (Appendix Figure D.1), while total QALYs gained increased with total costs (Figure 5.1). Given a similar number of screens, total costs were higher when the total QALYs gained were higher, indicating that early detection of cancer and thus longer continuous phase care may contribute to an increase of costs. For example, the scenario—individual_adjusted_55_0.00493 (115,751 screens per 100,000 population) had similar number of screens as biennial screening (117,974 screens per 100,000 population), while the total QALYs gained compared with no screening and the total costs of the

"individual_adjusted_55_0.00493" scenario (QALYs gained: 1,713; total costs: $326,349,084) were higher than those of biennial screening (QALYs gained: 1,663; total costs: $325,700,621) (Appendix Table D.1). The major difference in the costs of these two scenarios came from the costs for stage I NSCLC, especially in the continuous phase costs (Figure 5.2 (A) & (B)). Scenarios that were at or close to the cost-effectiveness efficient frontier were mostly individualized schedules (Figure 5.1). By-pack-year schedules have slightly worse benefits than individualized schedules given similar costs, but better than schedules selected by sex or for the whole population. Biennial and triennial screening did not achieve as much health benefits as individualized schedules given similar total costs.

The 25 scenarios at or near the efficient frontier for QALYs gained given a number of LDCT screens consisted of mostly individualized screening schedules (18), triennial screening, schedule selected by pack years (3) or by sex (1), annual screening, and no screening (Table 5.1). Annual screening had the highest total costs ($364 millions), highest total life years (2,824,876) and QALYs (2,349,128). Irrespectively of the schedule, lung cancer screening was found to be cost-effective. Compared with no screening, the costs per quality adjusted life year (QALY) gained ranged from $33,116 to $43,341, and the costs per life year gained ranged from $25,320 to $33,656. We identified 9 dominant strategies among the 141 considered, with 6 being individualized schedules, 2 by-pack-year schedules and 1 by annual screening. Other schedules, including biennial and triennial screening, had higher costs but lower or equal QALYs gained than at least one of the dominant strategies (dominated or weakly dominated). The incremental cost-effectiveness ratios per QALY ranged from $33,116 to $120,487. The most cost-effective strategy under the WTP threshold of $100,000 was the "bypky_adjusted_55_0.00293" schedule, with an ICER being $80,746. This strategy would screen individuals with 30-39 pack year

history at ages 55, 58, 60, 62, 64, 66, 67, 68, 70, 71, 72, 73, 74, 76, 78, and 80, and individuals with 40+ pack year history annually. The ICER of annual screening was $120,487, and thus was not cost-effective compared with previous dominant scenario under the $100,000 WTP threshold. The cost-effectiveness results for all scenarios are presented in Appendix Table D.1.

According to the one-way sensitivity analysis, varying the screening costs (LDCT examination costs) to be 15% below or above the base-case value had greater impact on the ICERs, compared with varying the continuous phase care costs for stage I NSCLC and the terminal phase costs for stage IV NSCLC (Table 5.2). Although the ICERs may decrease or increase by $1,300 to $14,700 in the one-way sensitivity analysis, annual screening remained not cost-effective in comparison with the most cost-effective adaptive screening strategies under the $100,000 WTP threshold. For sensitivity analysis scenarios that favor screening: lower screening costs, lower stage I cancer care costs, and higher stage IV cancer care costs, the "bypky_unadjusted _55_0.00293" schedule, which was more intensive than the "bypky_adjusted _55_0.00293" schedule, was the most cost-effective strategy. For "anti-screening" scenarios, the "bypky_adjusted _55_0.00293" schedule remained the most cost-effective strategy.

Based on the probabilistic sensitivity analysis, annual screening had 0% probability of being cost effective under the $100,000 WTP threshold (Figure 5.3). However, if the WTP threshold increased to $150,000 per QALY, the ICER of annual screening would be lower than the threshold with a probability of 100%, and thus became the most cost-effective strategy. The "bypky_adjusted _55_0.00293" schedule remained the most cost-effective strategy under the $100,000 WTP threshold in 100% of the 100,000 iterations. The "individual_adjusted_55_0.00793" schedule remained on the efficient frontier in 64% of the 100,000 iterations, while other dominant strategies remained on the efficient frontier with over

95% of the iterations. Compared with no screening, the costs per QALY gained for the nine dominant strategies were all under $50,000 in 100% of the probabilistic sensitivity analysis (PSA) iterations (Appendix Figure D.2).

5.4 Discussion

We examined the cost-effectiveness of adaptive and regular non-adaptive (i.e., triennial, biennial and annual) screening schedules for lung cancer. All strategies considered had costs per QALY gained lower than $50,000 compared with no screening, implying that lung cancer screening, regardless of screening schedules, is cost-effective. However, compared with efficient adaptive schedules, triennial and biennial screening were weakly dominated, whereas annual screening had an ICER of $120,000 and a 100% probability being over the $100,000 WTP threshold. Hence, the adaptive schedules selected by the threshold methods may be more cost-effective than regular non-adaptive schedules. Nonetheless, annual screening was found to have a 100% probability of being the most cost-effective under a $150,000 WTP threshold.

Previous cost-effectiveness analysis of lung cancer screening found that annual screening under the 2013 USPSTF eligibility guidelines was cost-effective in the United States, with the costs per QALY gained being $45,800 compared with no screening.[30] Another cost-effectiveness analysis conducted in Canada also identified annual screening under the 2013 USPSTF guidelines to be cost-effective with the costs per life years gained being CAD $45,916.[146] Our estimates for annual screening are consistent with these findings. The evidence in the literature on the cost-effectiveness of biennial screening is mixed: one study found biennial screening to be more cost-effective than annual screening,[147] while another found biennial screening to be less cost-effective than the annual screening.[146] Our study results suggest biennial screening is not cost-effective compared with the adaptive schedules and annual screening.

Despite similar strengths and limitations for the threshold method as those discussed in Chapter IV, we have some specific limitations specifically for this cost-effectiveness study. First, we did not consider indirect costs, such as work loss and reduced productivity due to attending screening and follow-up procedures and earlier detection of lung cancer. Early detection of lung cancer may lead to lower treatment but higher long-term care costs, which was directly accounted for in our analysis. Adding indirect costs may inflate the overall ICERs for all scenarios, and may favor less intensive screening schedules. In addition, we did not consider the fixed costs of starting a screening program, including the costs for screening program infrastructure, staff training and advertising.[146] Adding these fixed costs will inflate the total costs of all strategies, but should not affect the values and rankings of the ICERs.

Second, our study did not consider the costs and survival benefits of immunotherapy for advanced non-small cell lung cancer (NSCLC) due to lack of population-based data on adoption, costs and their efficacy. The treatment landscape for advanced NSCLC is quickly changing with the introduction of immunotherapy.[148] Immunotherapy was recently approved by FDA as the first-line treatment for advanced (stage IV) NSCLC patients with certain tumor characteristics in 2016, with an expansion of eligibility in 2019.[148,149] Although immunotherapy has been shown to improve overall survival and progression-free survival, it has significantly higher costs than standard care.[148,150,151] Therefore, most economic studies found that immunotherapy might not be cost-effective under the WTP threshold of $100,000/QALY.[150,151] On the other hand, our lung cancer-specific survival was estimated using SEER 2010-2014 data, and thus did not reflect the survival benefits of immunotherapy.[29] It is unclear how incorporating immunotherapy may change the ICERs of our scenarios. However, since immunotherapy is restricted to advanced

stage cancers, and screening results in early detection and a shift to earlier stages, it is likely that considering immunotherapy costs would result in improvements in the cost-effectiveness for screening. Future cost-effectiveness studies of lung cancer screening need to consider the costs and survival impact of immunotherapy as more population-based data become available.

Third, we did not vary adherence rate in the sensitivity analysis. Previous cost-effectiveness analysis studies found that decreasing adherence rate would reduce the ICER of lung cancer screening.[30,146,152] As the modeling approach in these studies were similar to ours, we would expect a similar impact of lower adherence rate on our ICERs. Therefore, when the adherence rate is low, more intensive schedules, such as annual screening, may become cost-effective under the current $100,000 WTP threshold. Finally, because it is computationally challenging to vary all model parameters, especially in the PSA, we varied only costs and utilities in our scenario-based sensitivity analysis and PSA.

In conclusion, some adaptive schedules were cost-effective based on a common U.S. WTP threshold. The probability of these schedules being cost-effective were over 95% after considering the uncertainty of costs and utilities. Annual screening was not cost-effective under the $100,000 WTP threshold, compared with the adaptive schedules. Hence, in a fixed budget health care system, adaptive schedules could provide better “value for the money” and should be considered.

5.5 Tables and figures

Table 5.1. Summary of cost-effectiveness results for the top 25 scenarios at or near the efficient frontier of quality-adjusted life years given number of screens for the 1960 US birth cohort

Scenario	Number of screens*	Total costs, USD*	Total life years*	Total quality-adjusted life years (QALYs)*	Costs per unit gained compared with no screening		ICER compared with previous efficient scenario	
					Per LY	Per QALY	Per LY	Per QALY
NoScreen	0	262,158,077	2,821,853	2,346,781	NA	Na	NA	Na
Individual_adjusted_0_0.0101	43,918	293,110,205	2,823,047	2,347,690	25,924	34,050	ED^	ED
Individual_adjusted_0_0.00993	44,934	293,671,869	2,823,098	2,347,733	25,320	33,116	25,320	33,116
Individual_adjusted_0_0.00893	53,235	298,158,875	2,823,261	2,347,863	25,573	33,267	27,507	34,367
Individual_adjusted_55_0.0101	54,988	298,787,279	2,823,242	2,347,853	26,373	34,180	D[&]	D
Individual_adjusted_0_0.00793	63,401	303,720,093	2,823,418	2,347,980	26,566	34,676	ED	ED
Individual_adjusted_55_0.00893	63,840	303,834,089	2,823,417	2,347,990	26,647	34,480	D	ED
Individual_adjusted_55_0.00793	73,362	308,186,197	2,823,557	2,348,096	27,020	34,990	ED	42,989
Individual_adjusted_0_0.00693	76,053	309,295,023	2,823,583	2,348,103	27,256	35,646	ED	ED
Triennial	81,675	309,658,303	2,823,561	2,348,107	27,826	35,814	D	ED
Individual_adjusted_55_0.00693	85,115	313,598,978	2,823,709	2,348,219	27,728	35,765	ED	ED
Individual_adjusted_0_0.00593	91,226	316,284,881	2,823,803	2,348,277	27,761	36,193	33,444	ED
Individual_adjusted_55_0.00593	99,241	319,684,715	2,823,874	2,348,342	28,467	36,846	ED	ED
Individual_adjusted_0_0.00493	108,657	322,610,165	2,823,948	2,348,405	28,867	37,218	ED	ED
Individual_adjusted_55_0.00493	115,751	326,349,084	2,824,067	2,348,494	29,004	37,465	ED	ED
Individual_adjusted_0_0.00393	129,374	330,346,524	2,824,207	2,348,609	28,973	37,302	ED	43,234
Individual_adjusted_55_0.00393	136,923	334,418,485	2,824,325	2,348,694	29,238	37,764	34,759	47,647
Individual_adjusted_55_0.00293	163,081	342,918,351	2,824,499	2,348,842	30,530	39,178	ED	ED
Individual_unadjusted_0_0.00293	188,002	349,959,842	2,824,662	2,348,962	31,259	40,262	ED	ED
Bypky_adjusted_55_0.00393	188,708	350,620,578	2,824,646	2,348,950	31,673	40,792	D	D
Individual_unadjusted_55_0.00293	193,722	352,563,261	2,824,719	2,349,011	31,545	40,549	45,995	57,407
Bypky_adjusted_55_0.00293	207,168	356,992,002	2,824,777	2,349,065	32,438	41,514	ED	80,746
Bypky_unadjusted_55_0.00293	217,940	360,295,471	2,824,828	2,349,098	32,990	42,351	71,060	100,531
Bysex_adjusted_55_0.00293	224,473	361,892,406	2,824,838	2,349,105	33,413	42,922	ED	ED

Annual	230,016	363,879,800	2,824,876	2,349,128	33,656	43,341	75,168	120,487

*Number per 100,000 total population alive at age 45; individuals were followed up from age 45 to 90
^ED: extended or weakly dominated
&D: dominated

Table 5.2. One-way sensitivity analysis results of dominant strategies for the 1960 birth cohort

Dominant scenarios	**ICER per QALY compared with previous efficient scenarios**						
	Base Case	LDCT examination Costs		Stage I NSCLC Continuous Phase Costs		Stage IV NSCLC Terminal Phase Costs	
		15% higher	15% lower	15% higher	15% lower	15% higher	15% lower
Individual_adjusted_0_0.00993	33,116	34,437	31,794	35,821	30,410	31,780	34,451
Individual_adjusted_0_0.00893	34,367	36,208	32,526	37,325	31,410	33,211	35,524
Individual_adjusted_55_0.00793^	42,989	46,017	39,961	45,500	ED*	41,795	44,183
Individual_adjusted_0_0.00393	43,234	46,365	40,103	46,336	40,240	42,114	44,354
Individual_adjusted_55_0.00393	47,647	51,173	44,121	49,579	45,715	46,669	48,625
Individual_adjusted_55_0.00293%	ED	ED	51,968	ED	ED	ED	ED
Individual_unadjusted_55_0.00293	57,407	62,714	52,215	60,581	54,232	56,535	58,279
Bypky_adjusted_55_0.00293	80,746	90,354	71,138	83,415	78,077	79,945	81,547
Bypky_unadjusted_55_0.00293	100,531	109,690	91,373	103,549	97,514	99,684	101,378
Annual	120,487	135,193	105,781	123,068	117,906	119,257	121,717

***** Ed: extended or weakly dominated
^ This strategy was weakly dominated only under the scenario when the costs for stage I NSCLC continuous phase were reduced by 15%, but dominant otherwise
% This strategy was dominant only under the scenario where LDCT examination costs were reduced by 15%, but weakly dominated otherwise

Figure 5.1. QALYs gained compared with no screening by the total costs for the 138 adaptive and 3 regular (non-adaptive) screening scenarios for the 1960 US birth cohort. The gray curve is the efficient frontier, connecting the dots with the highest QALY gained given the same total costs. Yellow dots represent regular screening: annual (circle), biennial (square), and triennial (triangle). Individualized schedules were highlighted in pink circle, by-pack-year schedules were colored in dark blue, by-sex schedules were colored in light green, while the schedules selected for the whole screen-eligible 1960 birth cohort were colored in light blue. Black crosses represented the 9 dominant strategies

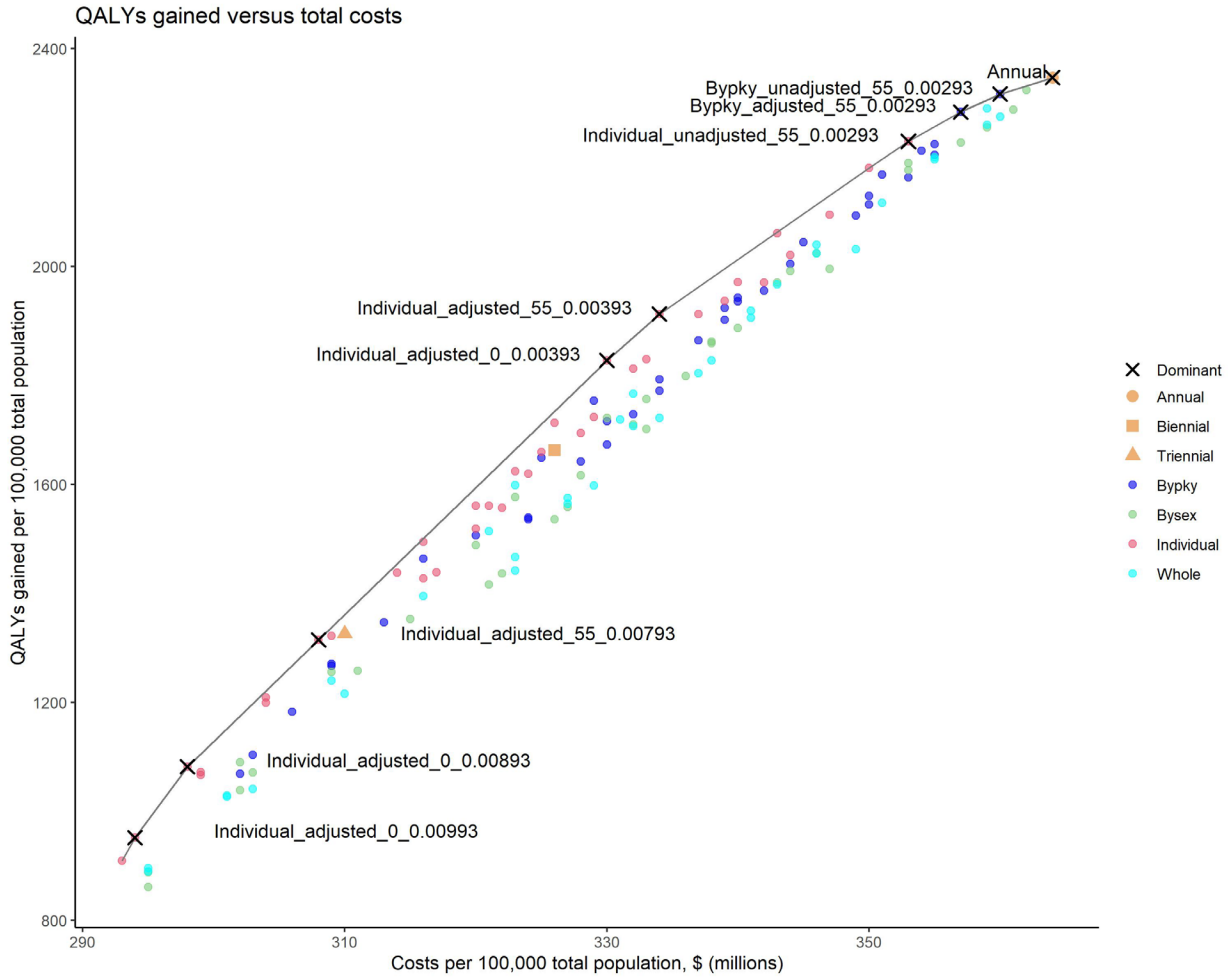
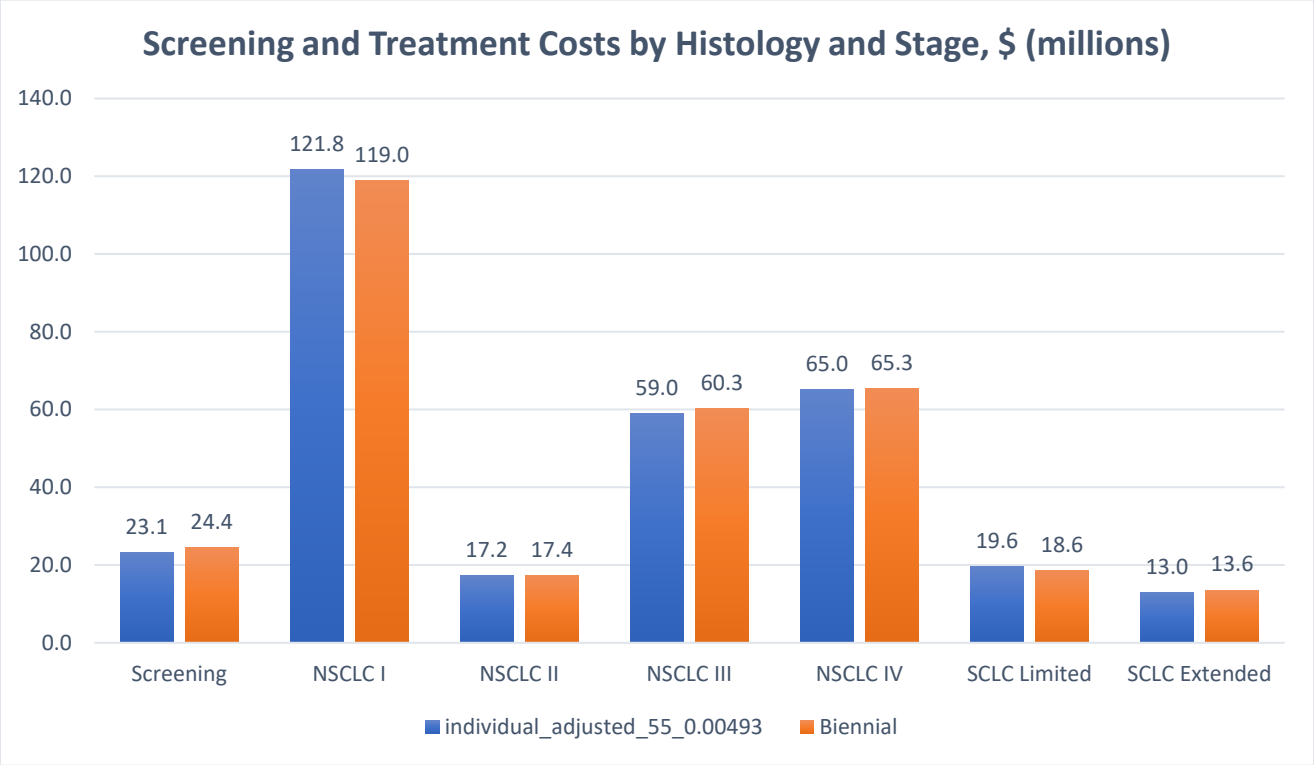


Figure 5.2. Comparison of screening and treatment costs for two scenarios with similar number of screens: individual_adjusted_55_0.00493 vs biennial. Figure 2 (A) shows the screening and treatment costs in millions by histology and stage for the two selected strategies; (B) shows the treatment costs in millions for the stage I NSCLC by phase (initial, continuous and terminal)

(A)



(B)

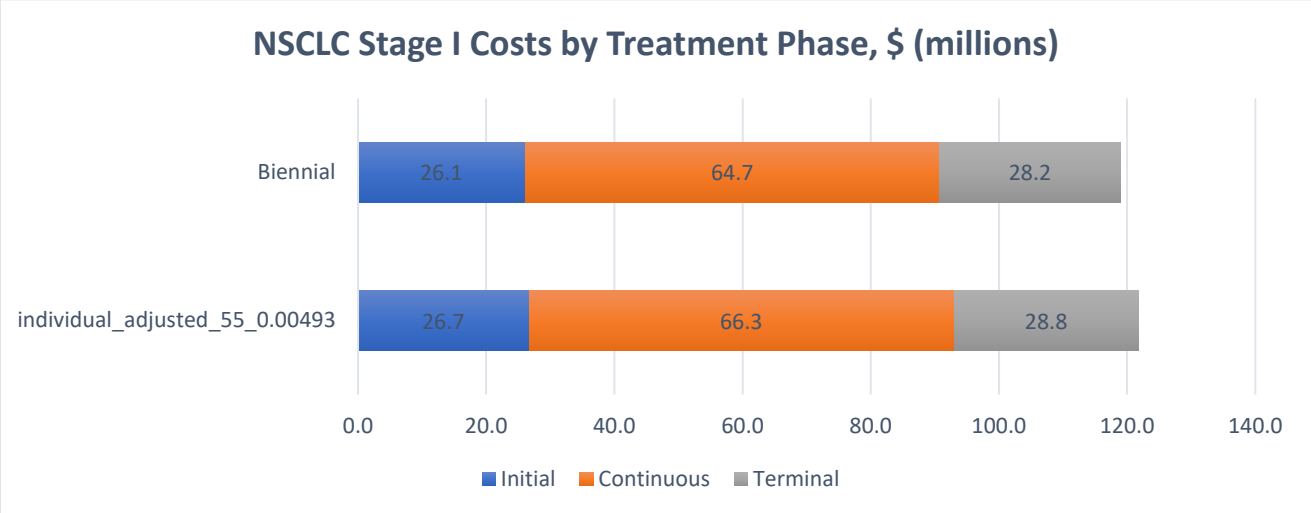
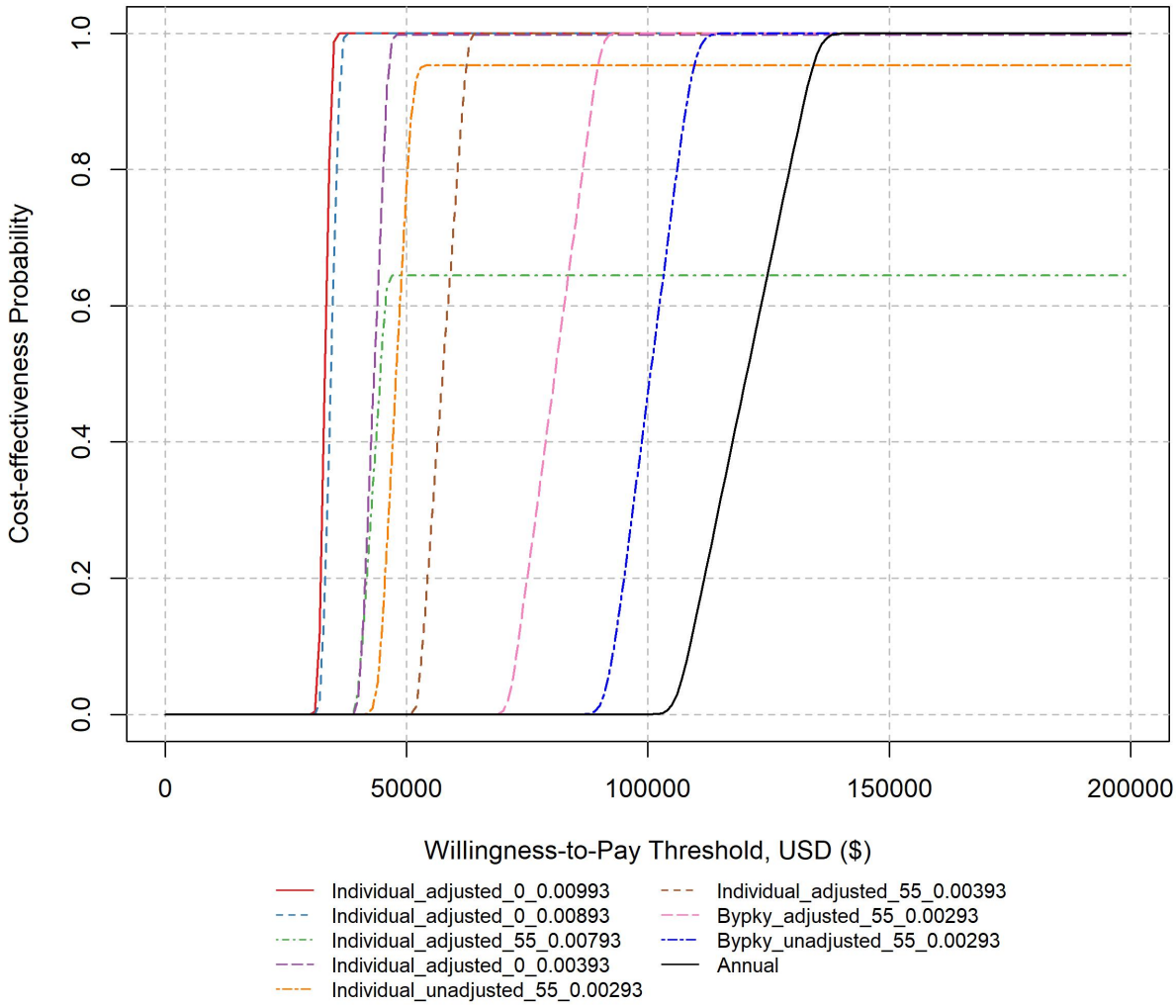


Figure 5.3. Cost-effectiveness acceptability curves for the 9 dominant strategies in the base-case analysis. The cost effectiveness of each strategy is calculated relative to the previous efficient strategy



Chapter VI

Conclusion

In this dissertation, I studied different strategies that could potentially enhance the impact of lung cancer screening by maximizing its benefits while reducing its associated harms, using a microsimulation modeling approach. Chapters II and III examined the effectiveness and cost-effectiveness of incorporating a primary lung cancer prevention strategy—a smoking cessation program—into the lung cancer screening program, while Chapter IV and V investigated the possibility of refining lung cancer screening schedules to achieve better benefit-to-harm ratio and screening cost-effectiveness.

Even though the US Preventive Services Task Force (USPSTF) started to recommend annual lung cancer screening (LCS) to eligible populations in 2013, and the Center for Medicare and Medicaid started to reimburse LCS in 2015,[11,153] the uptake of LCS in the US has been low so far. A study conducted in a large healthcare system in Northern California found the referral rate to LCS among eligible patients increased from 0.7% in 2013 to 2.8% in 2014, and to 7.3% in 2016.[154] Other studies found the uptake rate was less than 5% in 2015 in the whole US, using the US-representative National Health Interview Survey data.[155] A more recent study, which utilized the 2018 Behavioral Risk Factor Surveillance System data (a nationwide surveillance system), showed that 17.7% of the smokers who are eligible for screening by the USPSTF guideline received annual LCS.[156] However, another study using data from the American College of

Radiology Lung Cancer Screening Registry estimated a much lower rate of uptake, being 5% in 2018.[157]

Even though LCS uptake has increased in recent years, the current uptake is still unacceptably low. The reasons for the poor uptake can be discussed from both patient and provider perspectives. From the patient's perspective, lack of awareness, cost concerns and the stigma or fear of "cancer diagnosis" or "being blamed for smoking" are common barriers to initiating LCS.[61] Furthermore, since LCS programs may be available only in large health care systems, patients living in rural areas may have difficulty accessing the care.[61] On the other hand, health care providers may have skepticism towards LCS effectiveness, unfamiliarity with the most recent LCS guidelines, difficulty obtaining a patient's smoking history and thus determining eligibility, challenges in conducting shared decision-making visits, and difficulty managing positive results.[61] Education and awareness campaigns to address knowledge gaps and concerns of patients, provider training, improvement in smoking history documentation in the Electronic Medical Records (EMR), automatic eligibility reminder in EMR, and decision aid tools to guide shared decision-making discussion are potential strategies to help boost LCS uptake.[61,158,159]

However, given the current low uptake of lung cancer screening and limited medical resources, we should consider implementing additional strategies to enhance the impact of lung cancer screening among current participants, one of which is to incorporate an effective smoking cessation program in the context of LCS. Participants in the LCS program may have different characteristics from non-screen eligible smokers or screen eligible smokers who do not participate in LCS.[15] They tend to be older and hold distinct beliefs toward smoking and smoking cessation: be less concerned about health effects of smoking, and be less willing to quit.[15,160]

They might be more proactive in their health care, but at the same time may have been exposed to smoking interventions before and be more reluctant to quit.[15] On the other hand, LCS has been hypothesized to be a teachable moment to encourage behavioral change and increase the effectiveness of behavioral interventions.[15] Hence, to better understand how best to deliver a cost-effective smoking cessation intervention in the context of LCS, eight clinical trials under the Smoking Cessation at the Lung Examination (SCALE) collaboration are underway to test different smoking cessation strategies.[15–18]

While we await the results from these clinical trials, in this dissertation, I utilized a microsimulation modeling approach to study the synergic effects of smoking cessation interventions and LCS on lung cancer and all-cause mortality and life years gained, under various assumptions of cessation intervention efficacy and screening uptake (Chapter II). Adding a one-time cessation intervention into LCS program, even with the modest intervention efficacy, has the potential to enhance the impact of LCS by averting more lung cancer deaths and gaining more life years due to a reduction in other tobacco-related health conditions, compared with screening alone strategy. In Chapter III, I evaluated the cost-effectiveness of 5 prototypical cessation interventions at the first time of the annual LCS, using costs from Medicare and intervention efficacy from the literature. All five smoking cessation interventions delivered with LCS could potentially provide considerable benefits at reasonable costs, with the incremental cost-effectiveness ratios well below the $100,000 willingness-to-pay threshold.

Findings from Chapter II and III highlight and encourage the implementation of smoking cessation programs in the context of LCS. They provide some guidance on how to target limited healthcare resources. Other than spending resources to improve screening uptake, a more efficient strategy to increase impact might be to spend resources on improving smoking cessation

discussion at the shared decision-making visits prior to LCS to encourage participation in smoking cessation program, and improving the cessation intervention performance for LCS participants (the major goal of the SCALE trials).

In addition to incorporating smoking cessation interventions into the LCS setting, I examined another strategy—personalizing the screening scheduling—in Chapter IV and V. Inspired by the observations from clinical trials that individuals with previous negative lung cancer screen(s) are at lower risk of lung cancer[121,122] and thus longer interval to the next screen may be more suitable for them,[123] I adapted a risk-threshold method, initially developed by Zelen et al. for breast cancer screening,[36] to LCS. In this adaptation, I accounted for more risk factors than in its original implementation, including sex and smoking history, and life expectancy. Using this method, I was able to obtain the optimal screening schedules based on lung cancer risks, risk factors and life expectancy (adaptive schedules). I evaluated the benefits and harms of these adaptive schedules in Chapter IV and compared them with regular (non-adaptive) schedules—annual, biennial and triennial. I then assessed the cost-effectiveness of these adaptive and non-adaptive schedules in Chapter V. In Chapter IV, I identified several efficient adaptive schedules that could maintain the health benefits from annual lung cancer screening, but reduce the potential harms from screening, such as the reduction in false-positive cases and overdiagnosis. Moreover, these efficient adaptive schedules were also more cost-effective than regular (non-adaptive) schedules under the $100,000 willingness-to-pay threshold (Chapter V). Furthermore, patients' preferences towards screening also play an important role in the perceived benefits from screening; when preferences are low, adaptive schedules were preferred over annual screening.

The results in Chapter IV and V suggest another approach to refine the current LCS processes. The current recommendation of annual screening may not be suitable or necessary for every screen eligible smoker. The results indicate that in terms of benefit vs harm trade-offs and cost-effectiveness, screening schedules based on individual lung cancer risk and life expectancy may be preferable. These findings align with the current call for a more personalized cancer screening,[161–163] and serve as an example of how to translate risk estimates (lung cancer risk) into clinically practical recommendations (lung cancer screening schedule) and meaningful estimates of benefits (lung cancer deaths averted and life years gained) using simulation modeling approaches.

The findings from this dissertation thus underscore the importance of shared decision-making for LCS. During the shared decision-making visits, the benefits of smoking cessation could be discussed and a referral for cessation intervention could be issued. In addition, the patient's preferences or attitudes towards screening should also be discussed, as the preferences may impact the overall gains from LCS. The pros and cons of the adaptive schedules could also be addressed during this visit. If the patient opts for less intensive screening, a personalized screening schedule can be provided at the time of the visit, and reminders for screening could be sent out electronically via SMS or email. However, this is a lot of information to be discussed during one short visit. Therefore, some strategies are needed to facilitate this process. For example, the patient could complete questionnaires regarding his/her basic medical information, smoking history, and attitude towards screening prior to the visit. In addition, a decision aid tool, similar to the previously validated web-based screening tool: shouldiscreen.com,[158,159] could be developed to facilitate the discussion. Some important elements of the decision aid should include an overview of the patient's risk profile (age, sex, smoking history, etc.) and preferences

towards LCS (e.g., on a scale 1 to 10), which will be embedded into a calculator for lung cancer risk and life expectancy, providing schedule recommendations based on risks and preferences.

On top of findings with important and practical public health implications, this dissertation uses innovative methodologies that can be applied in other areas of study. I used a microsimulation modeling approach to answer counterfactual questions that have not yet been answered or may not realistically answerable by clinical trials, because of either ethical or financial reasons. The microsimulation modeling approach has been widely used in the field of cancer epidemiology, especially for numerous studies under the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium (e.g., breast, cervical, colon, esophageal, lung and prostate cancer).[13,25–27,131,132,164–166] I utilized public data and studies to update and extend the lung cancer natural history and screening model, and validated it against lung cancer incidence and mortality data from nationally representative health surveys and clinical trials.[13,29,52] However, the novel smoking cessation component incorporated in the model for Chapter II and III has not yet been validated. Once the SCALE trials are published, we will utilize the trial data to validate the model. Furthermore, in Chapter IV and V, we assumed that the LCS sensitivity and specificity do not vary with the screening schedules. Although this is a reasonable assumption, emerging data from different studies, including the 4-IN-THE-LUNG-RUN clinical trial (a European multi-country lung cancer screening trial) could be used to fine-tune the model.[134] Furthermore, I adapted a risk-threshold method for lung cancer screening to identify optimal screening schedules. This method could be extended to other cancers, such as cervical and colorectal cancers, and similarly we could then determine the clinical benefits of adaptive schedules with the help from validated simulation models for these cancers

Furthermore, a microsimulation model may consist of multiple "smaller" sub-models, either mathematical and/or statistical, to simulate the whole process designed to achieve the study objective (e.g., generating the natural history of lung cancer). It is important to have a clear overarching framework for the microsimulation model to guide model-building before diving into each detailed component in the model. It is necessary to make sure the "smaller" sub-models are well-calibrated—model results can reflect observed patterns—before integrating them into the full natural history model. After "assembling" the full natural history model, additional validation is needed to test model performance on external data, such as national level data on lung cancer incidence and mortality.[20,29]

All in all, there are gaps remaining between screening guidelines and optimal implementation of lung cancer screening. This dissertation provides some potential solutions to fill in some of these gaps and provides promising directions for future research.

Appendices

Appendix A

Supplementary Material for Chapter II

Table A.1. Percentage and number ever eligible for screening, and going through the smoking cessation intervention under screening uptake of 100%, 60%, 40% and 10%

	Birth Cohort 1950					Birth Cohort 1960				
Screening uptake	Percentage of cohort ever eligible for screening	Number* of people screened	Percentage of cohort ever eligible for screening as a current smoker	Number* of smokers going through the intervention	Number* of lung cancer deaths averted	Percentage of cohort ever eligible for screening	Number* of people screened per 100,000	Percentage of cohort ever eligible for screening as a current smoker	Number* of smokers going through the intervention	Number* of lung cancer deaths averted
100%	21.10%	21,060	16.00%	16,030	807	14.30%	14,320	11.10%	11,100	425
70%	21.10%	14,740	16.00%	11,220	549	14.30%	10,020	11.10%	7770	298
50%	21.10%	10,530	16.00%	8,010	402	14.30%	7,160	11.10%	5550	211
30%	21.10%	6,320	16.00%	4,810	244	14.30%	4,300	11.10%	3330	131
20%	21.10%	4,210	16.00%	3,210	158	14.30%	2,860	11.10%	2220	81
10%	21.10%	2,100	16.00%	1,600	80	14.30%	1,430	11.10%	1110	42

* Per 100,000 population at age 45

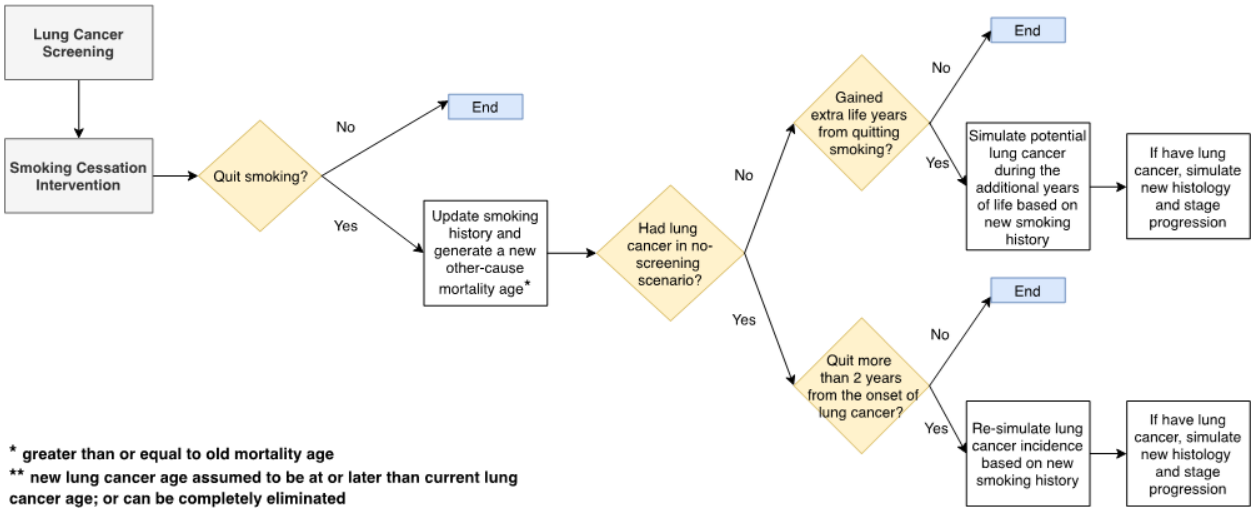
Table A.2. Lung cancer deaths averted per 100,000 screened individuals (by selected cessation probabilities and uptake) for 1950 and 1960 birth cohorts

Birth Cohort 1950						
Screening uptake	*Probability of Cessation due to Intervention*					
	0%	5%	10%	15%	20%	25%
100%	3,832	4,183	4,535	4,886	5,176	5,570
70%	3,725	4,227	4,512	4,830	5,142	5,529
50%	3,818	4,141	4,549	4,900	5,204	5,613
30%	3,861	4,066	4,399	4,794	5,332	5,538
20%	3,753	4,204	4,489	4,632	5,036	5,487
10%	3,810	4,429	4,476	5,095	5,143	5,619
Birth Cohort 1960						
	0%	5%	10%	15%	20%	25%
100%	2,968	3,163	3,464	3,757	4,022	4,274
70%	2,974	3,224	3,453	3,713	4,072	4,341
50%	2,947	3,170	3,506	3,785	3,994	4,274
30%	3,047	3,140	3,628	3,767	4,000	4,279
20%	2,832	3,322	3,566	3,846	4,091	4,301
10%	2,937	3,217	3,427	3,776	4,126	4,266

Table A.3. Life years gained per 100,000 screened individuals (by selected cessation probabilities and uptake) for 1950 and 1960 birth cohorts

Birth Cohort 1950						
Screening uptake	*Probability of Cessation due to Intervention*					
	0%	5%	10%	15%	20%	25%
100%	57,374	82,692	106,838	130,370	154,668	179,938
70%	55,923	82,341	106,099	131,289	154,552	179,233
50%	57,075	81,519	106,961	130,123	155,916	180,465
30%	57,674	80,949	104,114	131,108	156,851	180,380
20%	55,938	81,663	104,466	129,026	152,898	176,081
10%	57,286	83,143	110,048	135,667	155,952	179,381
Birth Cohort 1960						
	0%	5%	10%	15%	20%	25%
100%	45,112	66,620	91,515	114,365	135,726	160,517
70%	44,711	67,715	90,499	114,611	137,385	161,966
50%	45,084	67,500	91,494	114,777	138,087	160,824
30%	46,465	67,465	93,814	114,233	137,512	158,837
20%	43,916	67,343	92,343	117,552	134,755	161,329
10%	47,343	68,951	91,818	113,217	138,741	158,182

Figure A.1. State-transition model of smoking cessation intervention simulation



Appendix B

Supplementary Material for Chapter III

B.1. Methods for the estimation of smoking cessation intervention effects

There is relatively scare data on effects of smoking cessation among participants in lung cancer screening. Since screen-eligible individuals are ages 55 and older, we searched for data on intervention effects from older individuals. We chose to estimate the relative risk of each intervention was based on data from Cochrane Reviews.[82–88,167] We first determined the pooled relative risk of NRT,[83] bupropion,[84] and varenicline[82] based on the prevalence of their use in the general population.[168–170] There was insufficient data to determine effects of each medication alone or with other interventions. For telephone counseling,[86] individual in-person counseling,[87] or group in-person counseling[88] with supplementary pharmacotherapy, we abstracted the relative risk of the intervention plus pharmacotherapy vs. a pharmacotherapy only control from Cochrane Reviews. For electronic/web-based interventions there was limited data that included pharmacotherapy in the Cochrane reviews,[45,85] so we used data from other studies that evaluated electronic/web-based interventions with pharmacotherapy compared to a pharmacotherapy control.

The relative risks of intervention plus pharmacotherapy vs. pharmacotherapy provide the marginal benefit of the intervention. We multiplied these relative risks by the pharmacotherapy relative risk to determine the relative risk of the intervention plus pharmacotherapy vs. minimal control.

The quit rate of a smoking cessation intervention was implemented in the model by applying the relative risk of a given intervention to the age and gender specific background smoking cessation rates in the University of Michigan's Lung Cancer Natural History and Screening Model.

Table B.1. Summary of smoking cessation intervention effectiveness

Intervention	**Relative Risk** (vs. Minimal Control)
Pharmacotherapy	1.93 (1.73-2.15)
Telephone Counseling plus Pharmacotherapy	2.20 (1.98-2.44)
Individual In-Person Counseling plus Pharmacotherapy	2.40 (2.15-2.66)
Group In-Person Counseling plus Pharmacotherapy	2.14 (1.92-2.38)
Electronic/Web-Based plus Pharmacotherapy	2.12 (1.90-2.36)

B.2. Smoking cessation intervention costing methodology

Intervention costs were calculated per participant from a societal perspective. As such, they consider the costs of counseling, drugs, and overhead associated with an intervention and the costs of a patient's time and travel. Time spent in a given intervention was averaged based on studies identified in a systematic review and meta-analysis of smoking cessation interventions and expert review.[45] We did not include time spent on patient outreach and recruitment in the estimation of intervention costs. Dollar values for all intervention components were derived from various sources:

- Wage rates were derived from the Bureau of Labour Statistics.[95]
- Travel costs were calculated based on research by the Pew Center on the average distance from medical services and the IRS medical mileage rate [14, 15].[98,99]
- Prescription fulfillment time for both pharmacists and intervention participants were from a time and motion study of pharmacists [16].[171]
- Pharmacotherapy costs are wholesale costs from the REDBOOK [17].[96]
- Space rental fees were the national average rental cost per square foot of medical office space in 2018. We assume that individual counseling will use 100 square feet of office space per counselor, 500 per group counselor, and 50 square feet per telephone counselor

[18].[100] Overhead and rental fees were then divided by the number of participants a counselor could see in a month assuming the intervention is at steady state.

- Phone charges were from the Bureau of Labor Statistics [19].[94]

All dollar amounts were inflated to 2019 dollars using the Bureau of Labor Statistics inflation rates from the medical care component of the consumer price index [20].[93]

The next section describes the intervention components and how they were costed and results are summarized on Table 2, below.

1. The costs included in a standard **pharmacotherapy intervention** includes a trip to a primary care provider who will assess an individual's suitability for pharmacotherapy and briefly counsel them to quit smoking. Costs for this visit are applied using CMS CPT codes. The base case assumes that a physician will bill for code 99212 (Evaluation and Management of an established patient <10 minutes) and 99406 (smoking cessation counseling 3-10 minutes). The lower estimate assumes a physician or nurse practitioner will bill code 99211 (Evaluation and Management of an established patient <5 minutes, may not require a physician) and 99406 (smoking cessation counseling 3-10 minutes). The upper estimate assumes a physician will bill for code 99212 (Evaluation and Management of an established patient <10 minutes) and 99407 (smoking cessation counseling >10 minutes).

Based on clinical guidelines, we assume that all participants will receive nicotine replacement therapy, bupropion, or varenicline proportional to their use in the general population (67% nicotine replacement, 22% varenicline, and 11% bupropion).[168–170] Participants received an 8-week course of nicotine replacement therapy (NRT) with a range of 6 to 10 weeks using a patch. Both Varenicline and Bupropion were prescribed for a 10-week course with a range of 8 to 12 weeks. We assumed that nicotine replacement therapy, bupropion, or varenicline costs

proportional to their use in the general population.[168–170] All fixed costs are assumed to be considered in the CMS reimbursement rate.

2. The costs involved in a standard **electronic/web-based intervention** include a pre-made online portal that allows users to browse educational materials, post in forums and receive prefabricated electronic messages (text or email) to promote cessation. We assumed a user would spend an hour (range 0.5-1.5 hours) using the service over the course of three (range 2-4 months). Website set-up fees are not included as they are considered research and development costs. The fees for hosting the website were assumed to be $1 per participant based on the intervention scale.[172] Rent, utilities, server hosting, website maintenance, and upkeep were all assumed to be included in this $1 fee. Based on the studies identified by a Cochrane Review meta-analysis, we assumed that electronic/web-based interventions did not provide pharmacotherapy directly to participants but we assumed that all participants would receive nicotine replacement therapy, bupropion, or varenicline from other sources proportional to their use in the general population.[168–170]

3. The costs of a standard **group in-person counseling intervention** were based on approximately seven sessions an hour in length with groups of eight participants. Counselors spent on average 0.86 (range 0.55-1.18) hours with each person allowing them to see approximately 186 participants in a month. We assumed that all participants received nicotine replacement therapy, bupropion, or varenicline proportional to their use in the general population.[168–170] Group counseling rent and utilities were low because the extra rental costs were distributed among the larger number of individuals taking part in the intervention each month.

4. The costs of a standard **individual in-person counseling intervention** involved time costs of approximately seven sessions an hour in length. Counselors spent on average 6.9 (range 4.41-9.4) hours with each person allowing them to see approximately 23 participants in a month. We assumed that all participants received nicotine replacement therapy, bupropion, or varenicline proportional to their use in the general population.[168–170]

5. Standard **telephone counseling interventions** have costs that include approximately five counseling calls of 11 minutes in length. We assumed a counselor spent approximately 1.04 (range 0.87-1.21) hours on counseling. The shorter counseling time reduced the costs to the participant and counselor per patient and allowed counselors to work with approximately 154 participants in a month. We assume that all participants received nicotine replacement therapy, bupropion, or varenicline proportional to their use in the general population.[168–170] Written materials and other intervention components were mailed to participants, so we included mail charges.

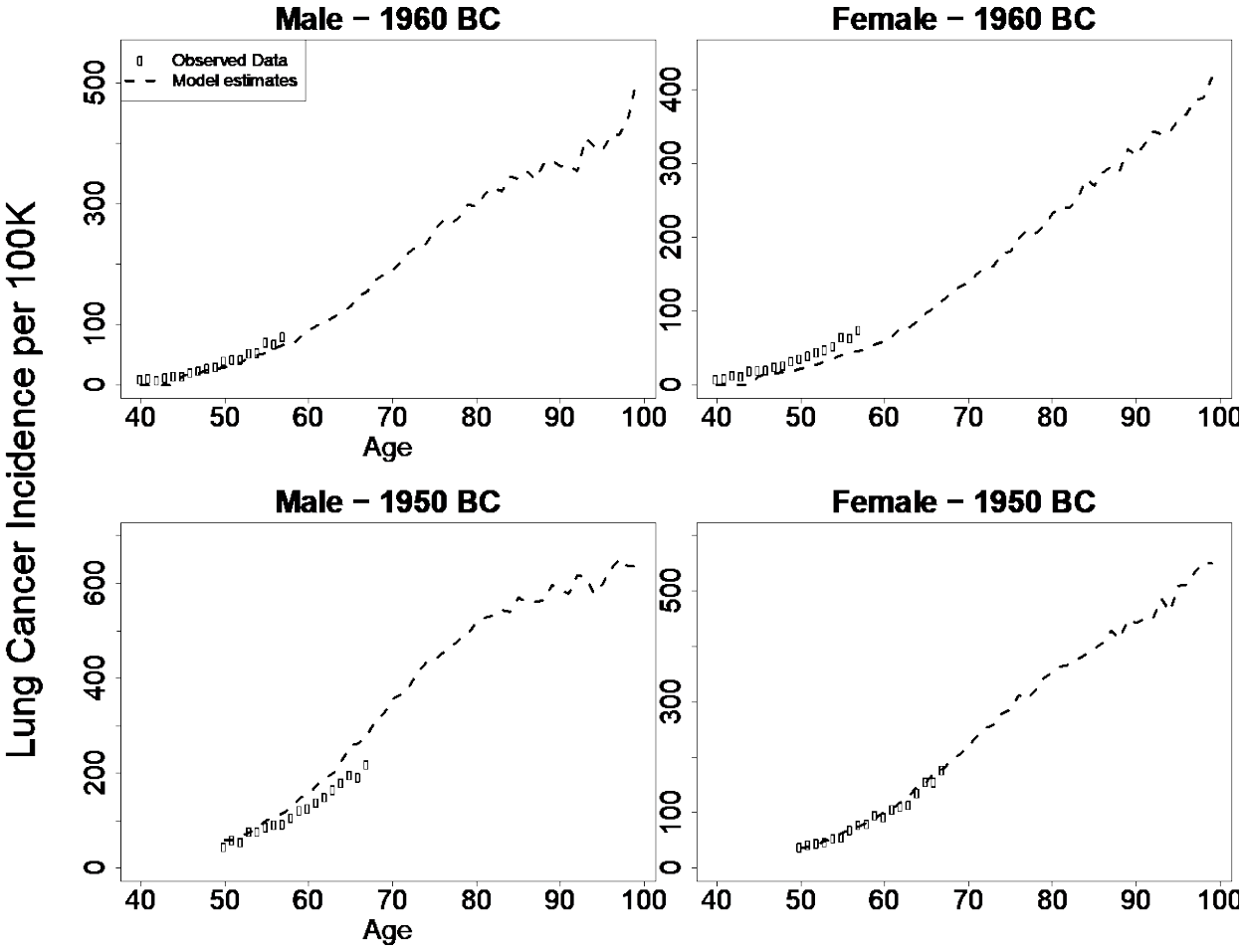
Table B.2. Smoking cessation intervention costs per patient

Cost Element	$/Patient					Sources
	Electronic/Web-Based[1]	Group In-Person Counseling[2]	Individual In-Person Counseling[3]	Telephone Counseling[4]	Pharmacotherapy[5]	
Variable Costs						
Staff Time						Bureau of Labor Statistics Wage Rates[95]
Counselors[6]	NA	$22 (12-34)	$175 (94-274)	$38 (28-48)	NA	
Pharmacist Time	$8 (6-10)	$8 (6-10)	$8 (6-10)	$8 (6-10)	$8 (6-10)	Frost et al, 2019[171]
Physician Visit	$61 (38-75)	$61 (38-75)	$61 (38-75)	$61 (38-75)	$61 (38-75)	Medicare reimbursement for a low-intensity physician visit plus tobacco counseling session[97]
Patient Time						Bureau of Labor Statistics Average Wage Rate[95]
Travel Time	$12 (8-16)	$100 (68-134)	$100 (68-134)	$12 (8-16)	$12 (8-16)	Assume 15 minutes of travel (10-20) each way[99]
Intervention Time	$34 (19-51)	$184 (118-251)	$184 (118-251)	$35 (28-44)	$9 (6-13)	
Prescription Fulfillment Time	$7 (6-9)	$7 (6-9)	$7 (6-9)	$7 (6-9)	$7 (6-9)	
Travel Costs	$6 (4-8)	$20 (12-36)	$20 (12-36)	$6 (4-8)	$6 (4-8)	Assume 5 miles of travel each way[99] using IRS medical mileage rate[98]
Pharmacotherapy Cost						Micromedex RedBook[96]
Nicotine Replacement	$123 (92-154)	$123 (92-154)	$123 (92-154)	$123 (92-154)	$123 (92-154)	8-week course (ranges from 6 to 10)
Varenicline	$140 (112-168)	$140 (112-168)	$140 (112-168)	$140 (112-168)	$140 (112-168)	10-week course (ranges from 8 to 12)
Bupropion	$39 (32-47)	$39 (32-47)	$39 (32-47)	$39 (32-47)	$39 (32-47)	10-week course (ranges from 8 to 12)
Mailing Fees[8]	NA	NA	NA	$8	NA	USPS Flat rate padded envelope[173]
Fixed Costs						
Rent & Utilities[9]	NA	$63 (40-84)	$100 (64-137)	$11 (10-12)	NA	Assumes 100 sq. ft. for Individual; 500 sq. ft. for

						group; and 50 sq. ft. for TC based on 23 Individual patients; 186 group patients and 154 TC patients per month[100]
Internet and Phone						
Staff Phone	NA	NA	NA	$3-4	NA	2019 landline charges assuming 3 months[94]
Website Maintenance and Hosting	$1	NA	NA	NA	NA	Fees related to website hosting at full scale are assumed to be $1 per person.
TOTAL COST	$431 (318-539)	$767 (536-1002)	$957 (642-1295)	$491 (375-603)	$405 (304-500)	

Figure B.1. Comparison of model projections to seer data 2000-2017 for age-specific lung cancer incidence and mortality by birth cohorts and gender

Panel A. Lung Cancer Incidence



Panel B. Lung Cancer Mortality

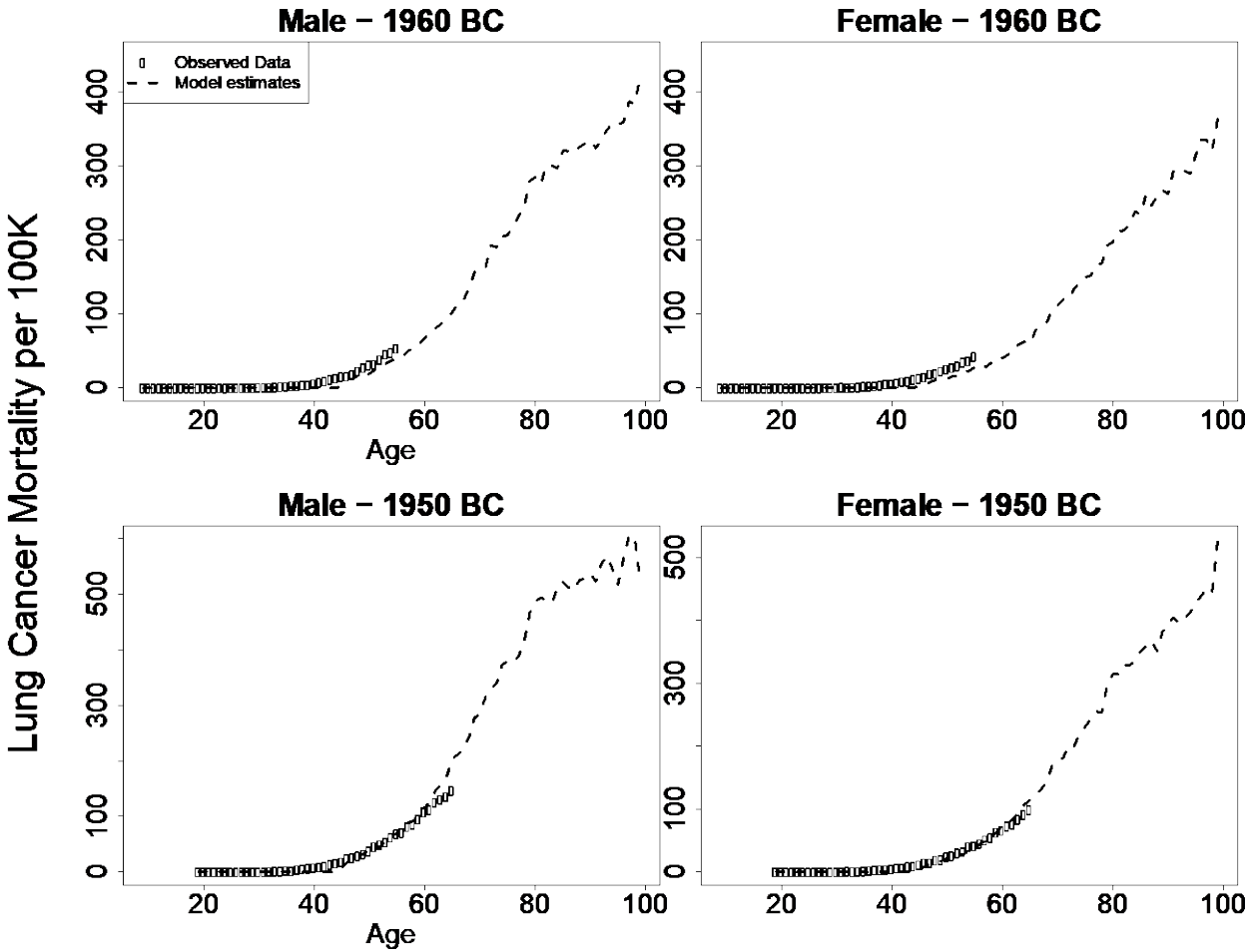


Figure legend: Panel A shows the comparison between model estimates of lung cancer incidence rate per 100,000 (dashed line) and Model was not calibrated to lung cancer incidence specifically. Panel B shows the age-specific mortality from lung cancer. The SEER data only extend to the current age of these birth cohorts, while the model projects over a lifetime.

Figure B.2. Efficiency frontiers of the incremental costs per quality adjusted life years gained from adding smoking cessation interventions to lung cancer screening: lowest and highest intervention effect

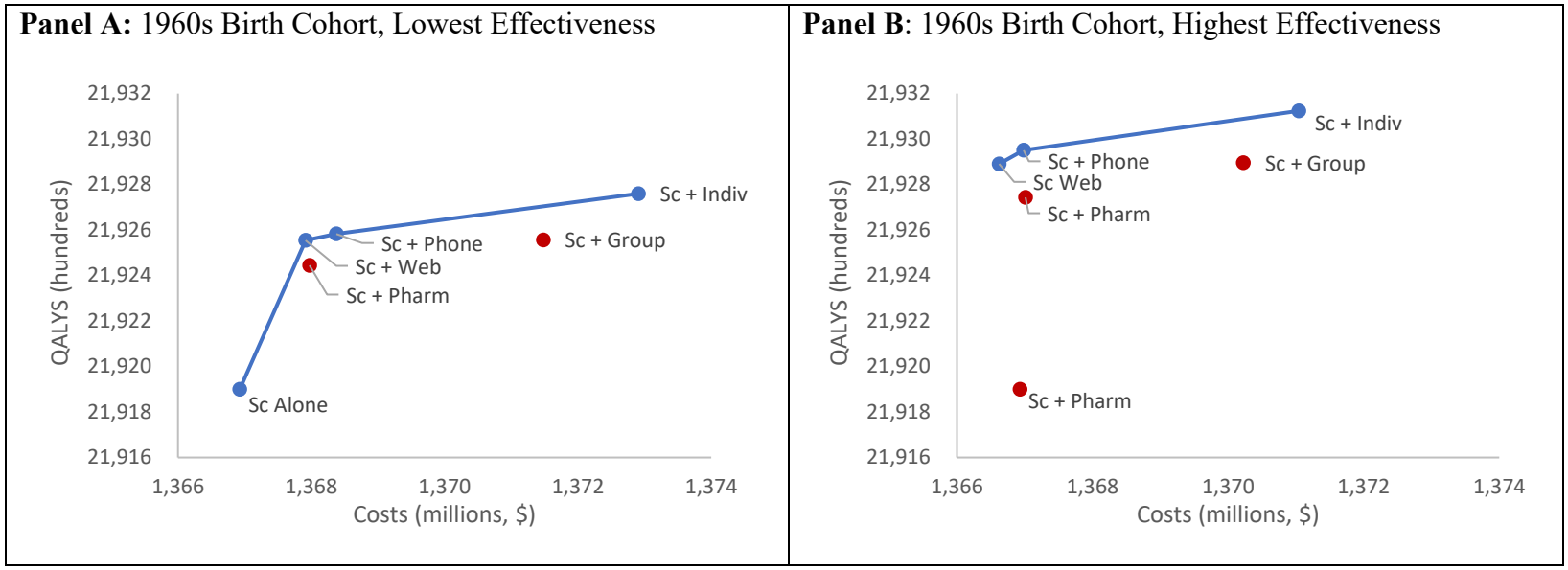


Figure legend: Strategies are screening plus no cessation (Sc Alone), screening plus pharmacotherapy (Sc + Pharm), screening plus electronic/web-based plus pharmacotherapy (Sc + Web), screening plus pharmacotherapy plus phone (Sc + Phone), screening plus group counseling plus pharmacotherapy (Sc + Group), and screening plus individual counseling plus pharmacotherapy (Sc + Indiv). Efficient strategies (those in blue that appear along the blue line) were those which yielded an increasing cost to benefit ratio; all other strategies (those in orange) are dominated.
Panel A presents the results for the 6 strategies using lowest intervention effectiveness in the 1960s birth cohort.
Panel B presents the results for the 6 strategies using highest intervention effectiveness in the 1960s birth cohort.

Table B.3. Results of one-way and multi-way sensitivity analyses on costs per quality adjusted life year of screening plus telephone counseling and pharmacotherapy compared to screening alone

Telephone Counseling and Pharmacotherapy	Incremental Costs vs Screening Alone ($)	Incremental QALYs vs Screening Alone	Costs ($) per QALY (ICER)
	Per 100,000 Screen-eligible Individuals[a]		
One-Way Analysis on Screening Coverage[b]			
Screening at 15%	893,337	877	1,019
Screening at 30%	1,637,968	1,722	951
Screening at 50%	2,422,333	2,811	862
Screening at 75%	2,712,168	4,175	650
Screening at 100%	4,245,364	5,515	770
One-Way Analysis on Intervention Costs[c]			
Lowest Costs	-358,339	878	-408
Base Case Costs	893,337	877	1,019
Highest Costs	2,101,882	878	2,394
Two-Way and Multi-Way Analyses on Intervention Costs and Effects			
Worst Case[d]	2,657,426	682	3,897
Base Case[e]	893,337	877	1,019
Best Case[f]	-1,196,023	1,050	-1,139
Ideal Case[g]	-10,342,829	6,643	-1,557

[a] Results are cumulative total lifetime costs and QALYs across the life course for 100,000 screen eligible individuals. Minus signs indicate savings in costs and QALYS.

[b] Screening plus telephone counseling and pharmacotherapy at each screening coverage level is compared to screening alone at the corresponding screening coverage level.

[c] Screening plus telephone counseling and pharmacotherapy at varying levels of costs are compared to screening alone. Screening coverage is set to 15%.

[d] Screening plus telephone counseling and pharmacotherapy at the highest costs and lowest effects compared to screening alone. Screening coverage is set to 15%.
[e] Screening plus telephone counseling and pharmacotherapy at the base case costs and base case effects compared to screening alone. Screening coverage is set to 15%.
[f] Screening plus telephone counseling and pharmacotherapy at the lowest costs and highest effects compared to screening alone. Screening coverage is set to 15%.
[g] Screening plus telephone counseling and pharmacotherapy at the lowest costs and highest effects compared to screening alone. Screening coverage is set to 100%.

Appendix C

Supplementary Material for Chapter IV

C.1. Life expectancy adjustment

We incorporate life expectancy into the threshold method in the following way. We first introduce some notations below.

Life expectancy at a specific age (A_0) or mean residual lifetime is defined as

$$m(A_0) = E(T - A_0 | T > A_0) = \frac{\int_{A_0}^{\infty}(t - A_0)f(t)dt}{P(T > A_0)} = \frac{\int_{A_0}^{\infty}(t - A_0)f(t)dt}{S(A_0)} = \int_{A_0}^{\infty}\frac{S(t)}{S(A_0)}dt,$$

where T is time to death, f(t) is the hazard of all-cause mortality rate, and S(t) is the survival function defined as S(t)=P(T>t).

We then use the mean residual lifetime to discount the age-specific lung cancer incidence rate, which is an input to the threshold method. Suppose the age at the first screen is t_0, the formula for the discounted lung cancer incidence rate $I_d(t)$ $(t \geq t_0)$ is given as

$$I_d(t) = \frac{m(t)}{m(t_0)}I(t)$$

We replace $I(t)$ with $I_d(t)$ as the input of age-specific incidence to the threshold method. We expect that the discounting will bring down the incidence for older ages, as the ratio, $\frac{m(t)}{m(t_0)}$, decreases with age. Hence, the schedule produced using the discounted incidence may be less frequent, especially in older ages, compared with the schedule produced using the original incidence.

Different mortality rates were applied for different population in our study. Average group-specific all-cause mortality rate were obtained for screen-eligible males and females, for 30-39 pack year and 40+ pack year groups, and for the whole screen-eligible population, using the other-cause mortality age output from the Smoking History Generator.[46,47] For individual

cases, we utilized an established other-cause mortality risk model to generate age-specific other-cause mortality rate to approximate all-cause mortality.[52]

Table C.1. Input parameters for the threshold method

Parameters	Description	Reference
Age-specific lung cancer incidence risk $I(t)$	We use the TSCE model, a dose-response mechanistic model that takes individual age-specific smoking history as input and generates individual age-specific lung cancer incidence risk TSCE model is based on age, sex, and smoking history As input to the threshold method, we need to aggregate the individual age-specific lung cancer incidence risk to get age-specific lung cancer incidence risk for the study populations (by sex and smoking history)	[31]
Preclinical lung cancer sojourn time distribution $w(t)$	We fit exponential distributions to the preclinical sojourn time (PST) output from the MichiganLung model, by gender and for the whole population Male exponential rate = 0.2971757 Female exponential rate = 0.2538838 Whole exponential rate = 0.2742169	
LDCT sensitivity β	LungRads: 84.9% at baseline, and 78.6% after baseline	[81]

Table C.2. Model parameters, utilities/disutilities and sources for the MichiganLung model

Parameters	Description	Reference
Lung cancer incidence risk	Using the TSCE model, a dose-response mechanistic model that takes age-specific smoking history as input and generates age-specific lung cancer incidence risk	[31]
Lung cancer histology	Using a multinomial logistic regression prediction model based on the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) control arm with sex, BMI, personal history of cancer, family history of lung cancer, history of COPD and smoking history as predictors	[29] appendix
Lung cancer stage	Distribution by histology and sex obtained from SEER 18, 2010-2014 data	[29] appendix
Preclinical sojourn time in the MichiganLung model	Weibull distribution with shape and scale parameters depending on sex, stage and histology using PLCO and NLST data	[34]
LDCT test detectability	Sensitivity of LDCT screen by stage, histology, and screening round; modified to reflect Lung-RADS Specificity of LDCT by screening round from Lung-RADS	[13,34,81]
Lung cancer specific mortality	Conditioned on sex, age group, histology and stage and using SEER 18 data and Cancer Survival Analysis software	[29] appendix
Other-cause specific mortality	Using the other-cause mortality age output from the Smoking History Generator	[46,47]
Utilities (quality of life)	Baseline and lung cancer-specific utilities by age	[30]
Disutilities	From lung cancer screening, follow-up tests if the screen is positive and related complications	[29]

Table C.1. Screening schedules selected by the threshold method by risk threshold and gender

MALE	Unadjusted_0_0.00293	50, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00293	50, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00393	52, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00393	52, 55, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00493	54, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00493	54, 57, 59, 61, 62, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00593	56, 58, 60, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00593	56, 59, 61, 63, 64, 66, 67, 68, 69, 70, 72, 73, 74, 75, 76, 77, 78, 79
	Unadjusted_0_0.00693	57, 60, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00693	57, 60, 63, 65, 66, 68, 69, 71, 72, 73, 74, 76, 77, 79, 80
	Unadjusted_0_0.00793	58, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00793	59, 62, 64, 66, 68, 70, 72, 73, 75, 76, 78, 80, 82
	Unadjusted_0_0.00893	59, 62, 64, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00893	60, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82
	Unadjusted_0_0.00993	60, 63, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00993	62, 65, 68, 70, 72, 74, 77, 79, 82
	Unadjusted_0_0.0101	60, 63, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.0101	62, 65, 68, 70, 72, 75, 77, 80, 82
	Unadjusted_55_0.00293	55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00293	55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00393	55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00393	55, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00493	55, 57, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00493	55, 58, 60, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00593	55, 58, 60, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00593	55, 58, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00693	55, 59, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00693	55, 59, 62, 64, 66, 67, 68, 70, 71, 72, 74, 75, 76, 78, 79
	Unadjusted_55_0.00793	55, 59, 62, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00793	55, 60, 63, 65, 67, 69, 70, 72, 74, 75, 77, 78, 80
	Unadjusted_55_0.00893	55, 60, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00893	55, 61, 64, 67, 69, 71, 72, 74, 76, 78, 80
	Unadjusted_55_0.00993	55, 61, 63, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00993	55, 62, 66, 68, 70, 73, 75, 77, 79, 82
	Unadjusted_55_0.0101	55, 61, 63, 65, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.0101	55, 62, 66, 68, 70, 73, 75, 77, 80, 83

FEMALE	Unadjusted_0_0.00293	50, 53, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00293	50, 53, 55, 56, 57, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00393	52, 55, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00393	52, 55, 57, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00493	54, 57, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00493	54, 57, 60, 61, 63, 64, 66, 67, 68, 69, 70, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00593	56, 59, 60, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00593	56, 59, 62, 64, 65, 67, 68, 70, 71, 72, 74, 75, 77, 78, 80
	Unadjusted_0_0.00693	57, 60, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00693	57, 61, 64, 66, 68, 69, 71, 73, 74, 76, 78, 79
	Unadjusted_0_0.00793	58, 61, 63, 65, 66, 67, 68, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00793	59, 63, 66, 68, 70, 72, 74, 76, 78, 80, 82
	Unadjusted_0_0.00893	59, 62, 64, 66, 67, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00893	60, 64, 67, 70, 72, 74, 77, 79, 82
	Unadjusted_0_0.00993	60, 63, 65, 67, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00993	62, 66, 69, 72, 75, 77
	Unadjusted_0_0.0101	60, 63, 66, 67, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.0101	62, 66, 69, 72, 75, 78
	Unadjusted_55_0.00293	55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00293	55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00393	55, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00393	55, 57, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00493	55, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00493	55, 58, 60, 62, 63, 65, 66, 67, 68, 70, 71, 72, 73, 74, 75, 76, 77, 78, 80
	Unadjusted_55_0.00593	55, 58, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00593	55, 59, 61, 63, 65, 67, 68, 70, 71, 72, 74, 75, 76, 78, 79
	Unadjusted_55_0.00693	55, 59, 61, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00693	55, 60, 62, 65, 67, 69, 70, 72, 74, 75, 77, 78, 80
	Unadjusted_55_0.00793	55, 60, 62, 64, 65, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00793	55, 61, 64, 66, 68, 71, 73, 74, 76, 79
	Unadjusted_55_0.00893	55, 60, 63, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00893	55, 62, 65, 68, 70, 73, 75, 77, 80, 83
	Unadjusted_55_0.00993	55, 61, 64, 66, 67, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00993	55, 63, 67, 70, 72, 75, 78
	Unadjusted_55_0.0101	55, 61, 64, 66, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.0101	55, 63, 67, 70, 73, 76, 78, 82

Table C.2. Screening schedules selected by the threshold method by risk threshold and pack-year category

30-39 PACK YEARS	Unadjusted_0_0.00293	53, 56, 58, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00293	53, 56, 59, 61, 63, 65, 66, 68, 69, 70, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00393	56, 60, 62, 64, 65, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00393	56, 60, 64, 66, 68, 70, 72, 73, 75, 76, 78, 79
	Unadjusted_0_0.00493	59, 62, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00493	60, 65, 68, 71, 73, 75, 77, 79
	Unadjusted_0_0.00593	61, 64, 67, 68, 70, 71, 72, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00593	64, 69, 72, 75, 78, 80
	Unadjusted_0_0.00693	63, 66, 69, 70, 72, 73, 74, 76, 77, 78, 79, 80
	Adjusted_0_0.00693	67, 72, 76, 80, 84
	Unadjusted_0_0.00793	64, 68, 70, 72, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00793	71, 76
	Unadjusted_0_0.00893	66, 69, 72, 74, 75, 76, 78, 79, 80
	Adjusted_0_0.00893	74
	Unadjusted_0_0.00993	67, 71, 73, 75, 76, 78, 79, 80
	Adjusted_0_0.00993	79
	Unadjusted_0_0.0101	67, 71, 73, 75, 77, 78, 79, 80
	Adjusted_0_0.0101	80
	Unadjusted_55_0.00293	55, 58, 59, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00293	55, 58, 60, 62, 64, 66, 67, 68, 70, 71, 72, 73, 74, 76, 78, 80
	Unadjusted_55_0.00393	55, 59, 61, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00393	55, 60, 63, 65, 68, 70, 71, 73, 75, 76, 78, 79
	Unadjusted_55_0.00493	55, 60, 63, 65, 67, 68, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00493	55, 62, 66, 69, 71, 74, 76, 78, 80, 82
	Unadjusted_55_0.00593	55, 62, 65, 67, 69, 70, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00593	55, 65, 69, 72, 75, 78
	Unadjusted_55_0.00693	55, 63, 66, 69, 70, 72, 73, 74, 76, 77, 78, 79, 80
	Adjusted_55_0.00693	55, 68, 72, 76, 80, 84
	Unadjusted_55_0.00793	55, 65, 68, 70, 72, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00793	55, 71, 76
	Unadjusted_55_0.00893	55, 66, 69, 72, 74, 75, 76, 78, 79, 80
	Adjusted_55_0.00893	55, 74
	Unadjusted_55_0.00993	55, 67, 71, 73, 75, 76, 78, 79, 80
	Adjusted_55_0.00993	55, 79
	Unadjusted_55_0.0101	55, 67, 71, 73, 75, 77, 78, 79, 80
	Adjusted_55_0.0101	55, 80
	Unadjusted_0_0.00293	49, 52, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00293	49, 52, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00393	51, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80

40+ PACK YEARS	Adjusted_0_0.00393	51, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00493	53, 55, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00493	53, 55, 57, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00593	54, 57, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00593	54, 57, 59, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_0_0.00693	55, 58, 60, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00693	55, 59, 61, 62, 64, 65, 67, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 79
	Unadjusted_0_0.00793	56, 59, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00793	57, 60, 62, 64, 66, 67, 68, 70, 71, 72, 74, 75, 76, 78, 79
	Unadjusted_0_0.00893	57, 60, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00893	58, 61, 64, 66, 67, 69, 70, 72, 73, 75, 76, 78, 80, 82
	Unadjusted_0_0.00993	58, 61, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.00993	59, 63, 65, 67, 69, 71, 73, 74, 76, 78, 80
	Unadjusted_0_0.0101	58, 61, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_0_0.0101	59, 63, 65, 67, 69, 71, 73, 74, 76, 78, 80
	Unadjusted_55_0.00293	55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00293	55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00393	55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00393	55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00493	55, 57, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00493	55, 57, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00593	55, 57, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00593	55, 58, 60, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Unadjusted_55_0.00693	55, 58, 60, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00693	55, 58, 60, 62, 64, 65, 66, 68, 69, 70, 71, 72, 73, 74, 76, 77, 78, 79, 80
	Unadjusted_55_0.00793	55, 58, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00793	55, 59, 62, 64, 65, 67, 68, 70, 71, 72, 73, 75, 76, 77, 79, 80
	Unadjusted_55_0.00893	55, 59, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00893	55, 60, 62, 64, 66, 68, 70, 71, 73, 74, 76, 77, 79
	Unadjusted_55_0.00993	55, 60, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.00993	55, 60, 63, 66, 68, 70, 71, 73, 75, 76, 78, 80
	Unadjusted_55_0.0101	55, 60, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80
	Adjusted_55_0.0101	55, 61, 64, 66, 68, 70, 72, 73, 75, 77, 79

Figure C.1. Probability of being in preclinical states given previous negative screens for two hypothetical individuals in the US 1960 birth cohort: (A) this individual started smoking at age 18, smoked 20 cigarettes per day and quit at age 60; (B) this individual started smoking at age 18, smoked 20 cigarettes per day and quit at age 48. The lung cancer risks were adjusted for life expectancy, and the screening started age was fixed at 55. The threshold for screening was set at 0.293%. Red circles indicated the continuous screening time selected by the threshold method. For person (A), the adaptive schedule resulted in 22 screens at ages 55.0, 56.5, 57.8, 58.9, 59.9, 60.8, 61.6, 62.4, 63.1, 63.7, 64.4, 65.6, 68.3, 69.4, 70.6, 71.8, 73.1, 74.3, 75.6, 76.9, 78.2, and 79.6; and for person (B), the adaptive schedule resulted in 22 screens at ages 55.0, 61.6, 65.8, 69.4, 72.7, 76.0, and 79.5. Hence, the discrete and unique screening ages for person (A) were 55, 56, 58, 59, 60, 61, 62, 63, 64, 66, 68, 69, 71, 72, 73, 74, 76, 77, 78, and 80; and 55, 62, 66, 69, 73, 76, and 80 for person (B)

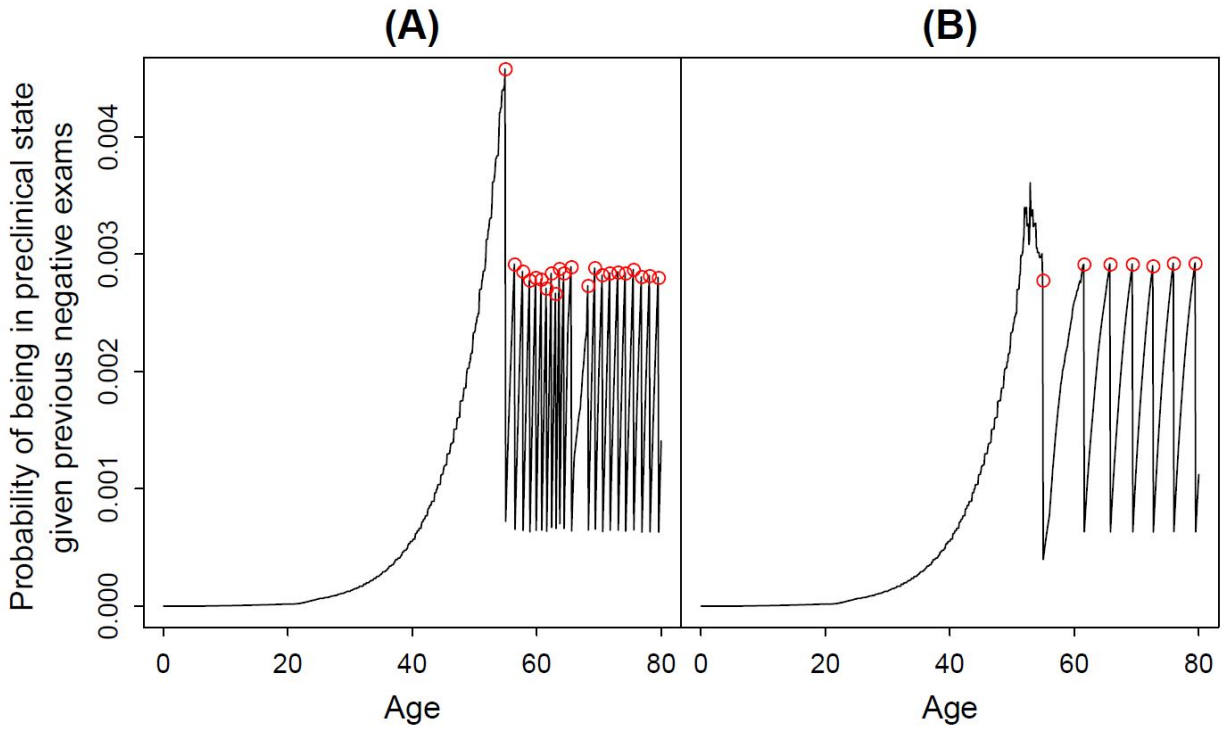


Figure C.2. Discounted quality adjusted life years (QALYs) gained compared with no screening by the level of disutilities and life expectancy adjustment. Scenarios adjusted for life expectancy were highlighted using blue circles, while unadjusted ones were highlighted using green circles. Black crosses highlighted the scenario(s) with the highest discounted QALYs, being (A) annual screening, (B) bypky_unadjusted_55_0.00293, (C) bypky_adjusted_55_0.00293, and (D) individual_adjusted_55_0.00793 and individual_adjusted_0_0.00593

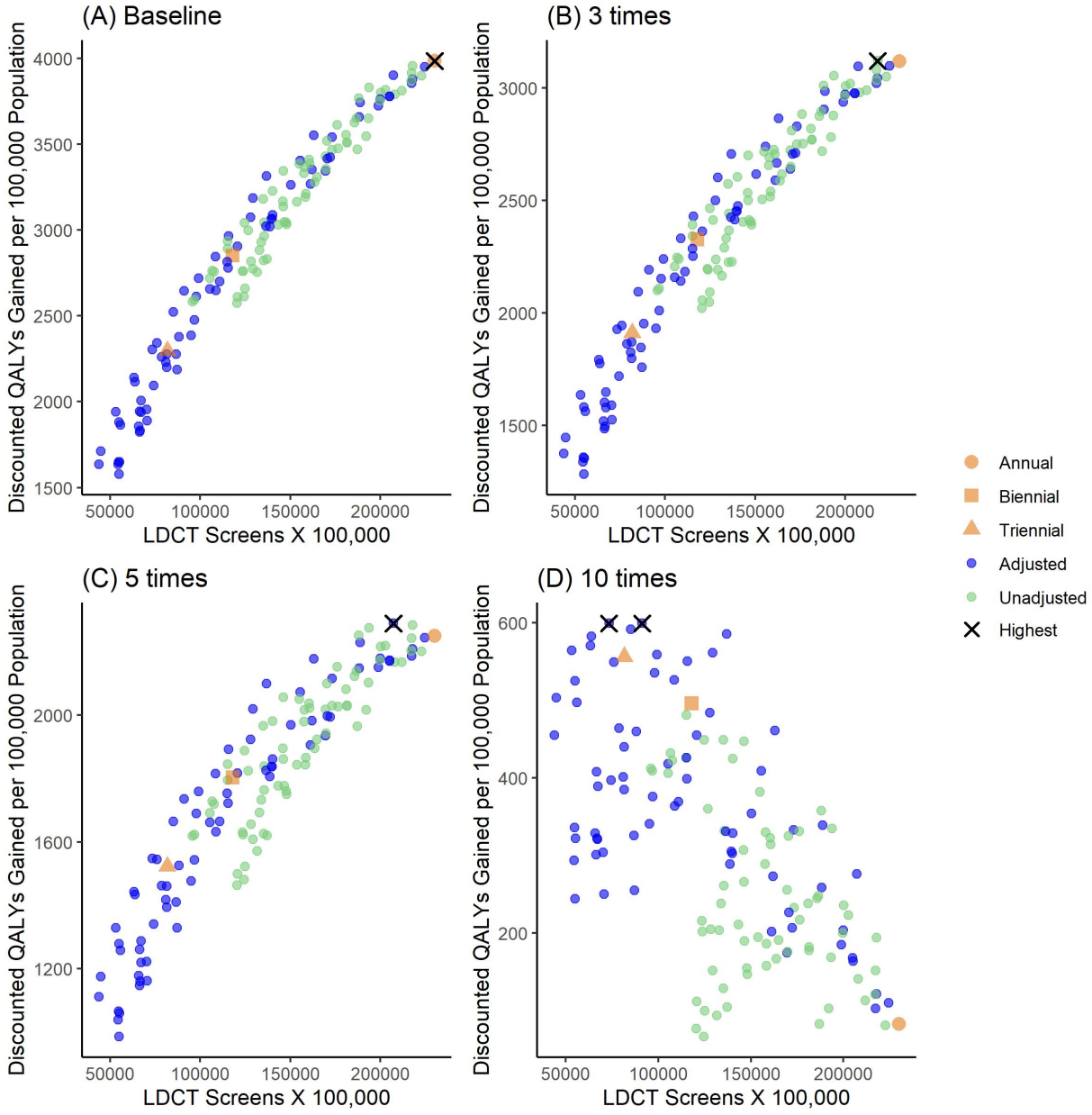
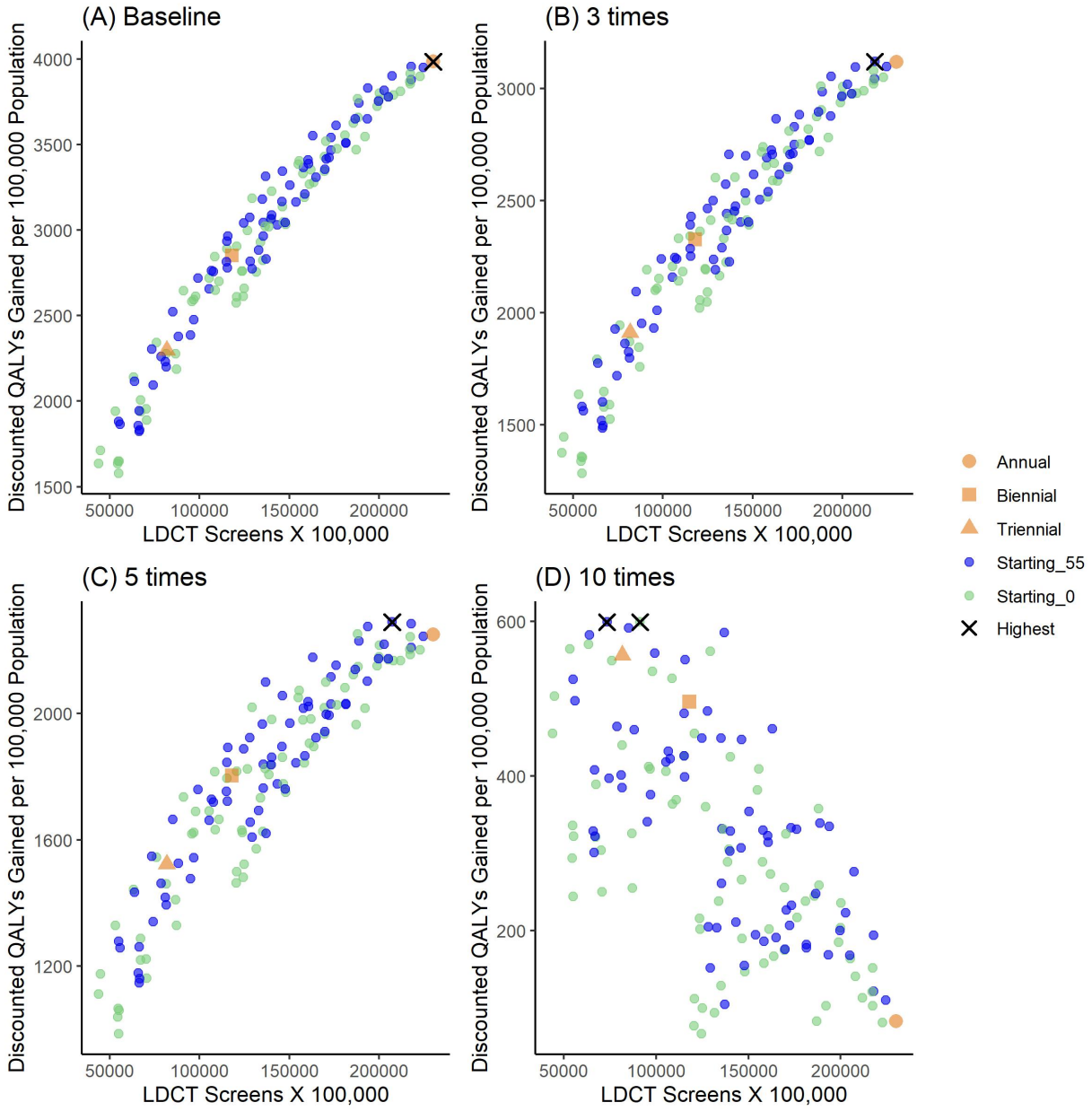


Figure C.3. Discounted quality adjusted life years (QALYs) gained compared with no screening by the level of disutilities and screening starting age. Adaptive schedules without fixing the starting age were highlighted using green circles, while the schedules with starting age fixed at 55 were highlighted using green circles. Black crosses highlighted the scenario(s) with the highest discounted QALYs, being (A) annual screening, (B) bypky_unadjusted_55_0.00293, (C) bypky_adjusted_55_0.00293, and (D) individual_adjusted_55_0.00793 and individual_adjusted_0_0.00593



Appendix D

Supplementary Material for Chapter V

Table D.1. Cost-effectiveness results of all 141 scenarios

Scenario	Number of Screens*	Total Costs, USD*	Total Life Years*	Total QALYs*	ICERs compared with Previous efficient strategy		Efficiency score^
					Per QALY	Per LY	
NoScreen	0	262,158,077	2,821,853	2,346,781	N	#N/A	1
individual_adjusted_0_0.0101	43,918	293,110,205	2,823,047	2,347,690	ED[%]	ED	0.997102
individual_adjusted_0_0.00993	44,934	293,671,869	2,823,098	2,347,733	33115.5	25319.71	1
individual_adjusted_0_0.00893	53,235	298,158,875	2,823,261	2,347,863	34367.22	27506.74	1
bysex_adjusted_0_0.0101	54,406	295,212,359	2,823,029	2,347,669	D	D	0.987608
whole_adjusted_0_0.0101	54,774	294,809,606	2,823,032	2,347,671	D	D	0.989212
individual_adjusted_55_0.0101	54,988	298,787,279	2,823,242	2,347,853	D	D	0.996684
bysex_adjusted_0_0.00993	55,052	295,094,884	2,822,988	2,347,642	D	D	0.984979
whole_adjusted_0_0.00993	55,197	295,286,821	2,823,040	2,347,677	D	D	0.98833
individual_adjusted_55_0.00993	55,909	299,103,202	2,823,237	2,347,848	D	D	0.995077
individual_adjusted_0_0.00793	63,401	303,720,093	2,823,418	2,347,980	ED	ED	0.998162
individual_adjusted_55_0.00893	63,840	303,834,089	2,823,417	2,347,990	ED	D	0.99922
bysex_adjusted_55_0.0101	65,953	301,540,473	2,823,215	2,347,820	D	D	0.983903
whole_adjusted_55_0.0101	66,421	301,305,530	2,823,197	2,347,810	D	D	0.983492
bysex_adjusted_55_0.00993	66,505	301,874,558	2,823,279	2,347,871	ED	ED	0.988804
whole_adjusted_55_0.00993	66,815	301,335,656	2,823,193	2,347,808	D	D	0.983197
bypky_adjusted_0_0.0101	67,260	302,468,231	2,823,258	2,347,850	D	D	0.984259
bypky_adjusted_0_0.00993	67,335	303,305,074	2,823,309	2,347,885	ED	ED	0.986156
bysex_adjusted_0_0.00893	70,284	303,162,387	2,823,266	2,347,852	D	D	0.982243
whole_adjusted_0_0.00893	70,605	302,837,465	2,823,223	2,347,822	D	D	0.979839
individual_adjusted_55_0.00793	73,362	308,186,197	2,823,557	2,348,096	42988.82	ED	1
bypky_adjusted_55_0.0101	74,367	306,177,734	2,823,392	2,347,964	D	D	0.98802
individual_adjusted_0_0.00693	76,053	309,295,023	2,823,583	2,348,103	ED	ED	0.997381

bypky_adjusted_55_0.00993	78,778	308,834,951	2,823,509	2,348,052	D	D	0.9917
bysex_adjusted_55_0.00893	81,105	309,388,909	2,823,497	2,348,037	D	D	0.987898
bypky_adjusted_0_0.00893	81,456	308,744,244	2,823,501	2,348,048	D	D	0.991436
whole_adjusted_55_0.00893	81,499	309,237,903	2,823,478	2,348,021	D	D	0.986117
Triennial	81,675	309,658,303	2,823,561	2,348,107	ED	D	0.996759
individual_adjusted_55_0.00693	85,115	313,598,978	2,823,709	2,348,219	ED	ED	0.999675
bysex_adjusted_0_0.00793	86,754	311,108,193	2,823,506	2,348,039	D	D	0.982732
whole_adjusted_0_0.00793	87,159	310,169,018	2,823,446	2,347,997	D	D	0.97981
bypky_adjusted_55_0.00893	88,240	312,554,061	2,823,602	2,348,128	ED	ED	0.990441
individual_adjusted_0_0.00593	91,226	316,284,881	2,823,803	2,348,277	ED	33443.89	0.999006
bysex_adjusted_55_0.00793	95,106	314,806,005	2,823,617	2,348,134	D	D	0.984061
individual_unadjusted_0_0.0101	95,893	316,004,056	2,823,725	2,348,209	D	ED	0.990698
individual_unadjusted_0_0.00993	96,799	316,528,638	2,823,743	2,348,220	D	D	0.990491
whole_adjusted_55_0.00793	96,888	315,965,183	2,823,677	2,348,176	D	D	0.986289
bypky_adjusted_0_0.00793	97,940	316,030,828	2,823,753	2,348,245	ED	ED	0.995487
individual_adjusted_55_0.00593	99,241	319,684,715	2,823,874	2,348,342	ED	ED	0.997276
individual_unadjusted_0_0.00893	105,287	319,987,520	2,823,840	2,348,300	D	D	0.990594
bypky_adjusted_55_0.00793	105,390	319,701,931	2,823,809	2,348,288	D	D	0.989914
individual_unadjusted_55_0.0101	106,685	321,276,534	2,823,892	2,348,342	ED	ED	0.99236
individual_unadjusted_55_0.00993	107,665	321,675,852	2,823,881	2,348,338	D	D	0.990571
individual_adjusted_0_0.00493	108,657	322,610,165	2,823,948	2,348,405	ED	ED	0.996674
bysex_adjusted_0_0.00693	108,768	319,806,922	2,823,796	2,348,270	D	D	0.987165
whole_adjusted_0_0.00693	110,983	320,878,378	2,823,826	2,348,295	D	D	0.987191
whole_adjusted_55_0.00693	115,131	323,241,359	2,823,930	2,348,380	D	D	0.991343
individual_unadjusted_0_0.00793	115,248	324,091,900	2,823,969	2,348,401	D	ED	0.991533
individual_unadjusted_55_0.00893	115,284	325,470,653	2,824,022	2,348,441	ED	ED	0.992716
bysex_adjusted_55_0.00693	115,492	323,125,970	2,823,901	2,348,358	D	D	0.988809
individual_adjusted_55_0.00493	115,751	326,349,084	2,824,067	2,348,494	ED	ED	0.997058
Biennial	117,974	325,700,621	2,824,000	2,348,444	ED	D	0.992377
bysex_unadjusted_0_0.0101	120,453	321,163,121	2,823,711	2,348,197	D	D	0.97312

bysex_unadjusted_0_0.00993	120,632	321,839,098	2,823,740	2,348,218	D	D	0.973935
bypky_adjusted_0_0.00693	120,684	325,252,260	2,823,990	2,348,430	ED	ED	0.991928
bypky_unadjusted_0_0.0101	123,505	323,989,644	2,823,868	2,348,320	D	D	0.980989
bypky_unadjusted_0_0.00993	123,796	324,469,356	2,823,858	2,348,317	D	D	0.979228
whole_unadjusted_0_0.0101	124,493	322,679,141	2,823,751	2,348,223	D	D	0.972078
individual_unadjusted_55_0.00793	124,747	328,539,382	2,824,103	2,348,505	ED	ED	0.991821
whole_unadjusted_0_0.00993	124,934	323,168,954	2,823,782	2,348,248	D	D	0.973908
individual_unadjusted_0_0.00693	126,767	328,436,612	2,824,063	2,348,475	D	D	0.988218
bypky_adjusted_55_0.00693	127,949	329,179,213	2,824,127	2,348,535	ED	ED	0.993772
whole_unadjusted_55_0.0101	128,310	326,782,334	2,823,925	2,348,356	D	D	0.977389
bysex_unadjusted_55_0.0101	129,260	326,555,628	2,823,896	2,348,340	D	D	0.976043
individual_adjusted_0_0.00393	129,374	330,346,524	2,824,207	2,348,609	43234.21	ED	1
bysex_unadjusted_0_0.00893	131,613	325,986,287	2,823,865	2,348,317	D	D	0.974688
bysex_unadjusted_55_0.00993	132,874	328,025,534	2,823,968	2,348,398	D	D	0.979309
bypky_unadjusted_0_0.00893	133,922	328,323,945	2,823,994	2,348,423	D	D	0.981633
individual_unadjusted_55_0.00693	135,039	332,051,408	2,824,201	2,348,594	D	D	0.992958
whole_unadjusted_0_0.00893	135,197	327,260,140	2,823,905	2,348,346	D	D	0.974626
bypky_unadjusted_55_0.0101	135,511	329,675,463	2,824,036	2,348,454	D	D	0.98175
bypky_unadjusted_55_0.00993	135,571	329,829,370	2,824,083	2,348,497	D	D	0.986929
bysex_adjusted_0_0.00593	136,552	330,496,385	2,824,092	2,348,503	D	D	0.985731
individual_adjusted_55_0.00393	136,923	334,418,485	2,824,325	2,348,694	47646.75	34759.18	1
whole_unadjusted_55_0.00993	137,070	328,723,214	2,823,941	2,348,379	D	D	0.974629
whole_adjusted_0_0.00593	138,745	331,272,284	2,824,088	2,348,500	D	D	0.982918
bypky_adjusted_0_0.00593	139,377	331,971,540	2,824,120	2,348,510	D	D	0.982194
bysex_adjusted_55_0.00593	140,023	332,500,335	2,824,133	2,348,538	D	D	0.98432
individual_unadjusted_0_0.00593	140,240	333,037,630	2,824,230	2,348,611	ED	ED	0.992266
whole_adjusted_55_0.00593	140,323	332,421,520	2,824,145	2,348,548	D	D	0.985831
bysex_unadjusted_55_0.00893	143,207	331,590,680	2,824,068	2,348,491	D	D	0.980806
bypky_unadjusted_55_0.00893	145,970	334,291,168	2,824,182	2,348,574	D	D	0.983631
individual_unadjusted_55_0.00593	146,175	336,575,942	2,824,337	2,348,694	ED	ED	0.993592

bypky_unadjusted_0_0.00793	146,191	334,090,228	2,824,162	2,348,553	D	D	0.981513
whole_unadjusted_0_0.00793	146,637	331,654,856	2,824,071	2,348,488	D	D	0.980244
whole_unadjusted_55_0.00893	147,789	333,777,141	2,824,097	2,348,503	D	D	0.976036
bysex_unadjusted_0_0.00793	148,000	332,782,896	2,824,079	2,348,483	D	D	0.976255
bypky_adjusted_55_0.00593	150,440	336,583,273	2,824,268	2,348,646	D	D	0.986658
bysex_unadjusted_55_0.00793	153,821	336,109,602	2,824,193	2,348,580	D	D	0.979094
individual_unadjusted_0_0.00493	154,925	338,522,113	2,824,362	2,348,718	ED	ED	0.991887
individual_adjusted_0_0.00293	155,627	340,166,337	2,824,403	2,348,753	ED	ED	0.993032
bypky_unadjusted_0_0.00693	157,613	338,854,881	2,824,319	2,348,683	D	D	0.985283
bypky_unadjusted_55_0.00793	157,933	339,042,425	2,824,351	2,348,705	D	D	0.988182
whole_unadjusted_0_0.00693	158,393	337,206,418	2,824,208	2,348,585	D	D	0.976554
whole_unadjusted_55_0.00793	158,538	337,548,283	2,824,224	2,348,609	D	D	0.978625
individual_unadjusted_55_0.00493	160,423	341,778,274	2,824,405	2,348,752	D	ED	0.988162
bypky_unadjusted_55_0.00693	160,828	340,116,054	2,824,370	2,348,724	ED	ED	0.988196
bysex_adjusted_0_0.00493	161,260	338,463,483	2,824,267	2,348,643	D	D	0.980812
bypky_adjusted_0_0.00493	161,988	340,486,831	2,824,356	2,348,717	D	D	0.985911
individual_adjusted_55_0.00293	163,081	342,918,351	2,824,499	2,348,842	ED	ED	0.999973
bysex_unadjusted_0_0.00693	163,696	338,363,600	2,824,264	2,348,640	D	D	0.980728
bysex_unadjusted_55_0.00693	164,943	339,948,826	2,824,298	2,348,668	D	D	0.980067
whole_adjusted_0_0.00493	169,431	341,019,623	2,824,321	2,348,687	D	D	0.979561
bypky_unadjusted_0_0.00593	169,575	342,095,380	2,824,388	2,348,737	D	D	0.984736
whole_unadjusted_55_0.00693	169,726	341,359,304	2,824,337	2,348,700	D	D	0.980649
individual_unadjusted_0_0.00393	170,398	343,887,119	2,824,472	2,348,802	D	D	0.990373
bysex_adjusted_55_0.00493	170,688	342,671,033	2,824,395	2,348,752	D	D	0.985603
whole_adjusted_55_0.00493	172,245	342,808,984	2,824,388	2,348,748	D	D	0.98453
bypky_adjusted_55_0.00493	173,130	344,918,479	2,824,492	2,348,826	D	D	0.991448
bypky_unadjusted_55_0.00593	173,245	344,355,812	2,824,440	2,348,786	D	D	0.986442
individual_unadjusted_55_0.00393	176,028	346,969,690	2,824,559	2,348,876	ED	ED	0.993911
bysex_unadjusted_0_0.00593	176,461	344,311,699	2,824,424	2,348,773	D	D	0.984315
whole_unadjusted_0_0.00593	180,964	346,174,889	2,824,491	2,348,821	D	D	0.987048

whole_unadjusted_55_0.00593	181,437	346,067,740	2,824,465	2,348,805	D	D	0.984687
bysex_unadjusted_55_0.00593	181,537	346,216,163	2,824,463	2,348,805	D	D	0.984249
bypky_unadjusted_0_0.00493	185,656	349,025,267	2,824,564	2,348,875	D	ED	0.987898
bypky_unadjusted_55_0.00493	186,585	349,679,044	2,824,588	2,348,895	ED	ED	0.989222
bysex_unadjusted_0_0.00493	187,069	346,889,141	2,824,428	2,348,777	D	D	0.977634
individual_unadjusted_0_0.00293	188,002	349,959,842	2,824,662	2,348,962	ED	ED	0.999439
bypky_adjusted_0_0.00393	188,157	350,118,983	2,824,595	2,348,911	D	D	0.990669
bypky_adjusted_55_0.00393	188,708	350,620,578	2,824,646	2,348,950	D	D	0.995569
whole_unadjusted_0_0.00493	192,151	348,702,780	2,824,477	2,348,813	D	D	0.978574
whole_unadjusted_55_0.00493	193,430	350,731,485	2,824,578	2,348,898	D	D	0.986729
individual_unadjusted_55_0.00293	193,722	352,563,261	2,824,719	2,349,011	57406.8	45995.09	1
bypky_adjusted_0_0.00293	198,916	353,242,209	2,824,640	2,348,945	D	D	0.987394
bysex_unadjusted_55_0.00493	199,593	352,946,015	2,824,654	2,348,958	D	D	0.990426
bysex_adjusted_0_0.00393/ bysex_adjusted_55_0.00393	199,913	353,164,315	2,824,663	2,348,971	D	D	0.991808
bypky_unadjusted_0_0.00393	200,201	353,826,007	2,824,701	2,348,994	D	D	0.993709
bypky_unadjusted_55_0.00393	202,764	354,945,742	2,824,712	2,349,006	D	D	0.992499
whole_adjusted_55_0.00393	204,989	354,790,282	2,824,683	2,348,978	D	D	0.988469
whole_adjusted_0_0.00393	205,213	355,091,819	2,824,687	2,348,982	D	D	0.988325
bypky_adjusted_55_0.00293	207,168	356,992,002	2,824,777	2,349,065	80746.31	ED	1
bypky_unadjusted_0_0.00293	207,974	355,412,135	2,824,685	2,348,986	D	D	0.988078
bysex_unadjusted_0_0.00393/ bysex_unadjusted_55_0.00393	211,908	357,082,466	2,824,714	2,349,009	D	D	0.987033
whole_unadjusted_0_0.00293/ whole_adjusted_0_0.00293	217,175	358,728,336	2,824,763	2,349,041	D	D	0.989775
bysex_adjusted_0_0.00293	217,294	358,897,861	2,824,755	2,349,037	D	D	0.988398
whole_unadjusted_0_0.00393/ whole_unadjusted_55_0.00393	217,328	359,220,719	2,824,793	2,349,071	ED	ED	0.995465
whole_adjusted_55_0.00293	217,885	359,607,159	2,824,775	2,349,056	D	D	0.990577
bypky_unadjusted_55_0.00293	217,940	360,295,471	2,824,828	2,349,098	100531.3	71059.82	1

bysex_unadjusted_0_0.00293	222,787	361,120,071	2,824,807	2,349,069	D	D	0.989481
bysex_adjusted_55_0.00293	224,473	361,892,406	2,824,838	2,349,105	ED	ED	0.997709
Annual	230,016	363,879,800	2,824,876	2,349,128	120487	75167.82	1

*** Number per 100,000 total population alive at age 45; individuals were followed up from age 45 to 90**
^ Efficiency scores ranging from 0 to 1 and obtained from the Data Envelopment Analysis. 1 indicates on the efficient frontier, while a number closer to 1 indicates the scenario is closer to the efficient frontier
% ED: extendedly or weakly dominated

Figure D.1. Total costs by the number of screens for the 138 adaptive and 3 regular (non-adaptive) screening scenarios for the 1960 US birth cohort. Yellow dots represent regular screening: annual (circle), biennial (square), and triennial (triangle). Individualized schedules were highlighted in pink circle, by-pack-year schedules were colored in dark blue, by-sex schedules were colored in light green, while the schedules selected for the whole screen-eligible 1960 birth cohort were colored in light blue

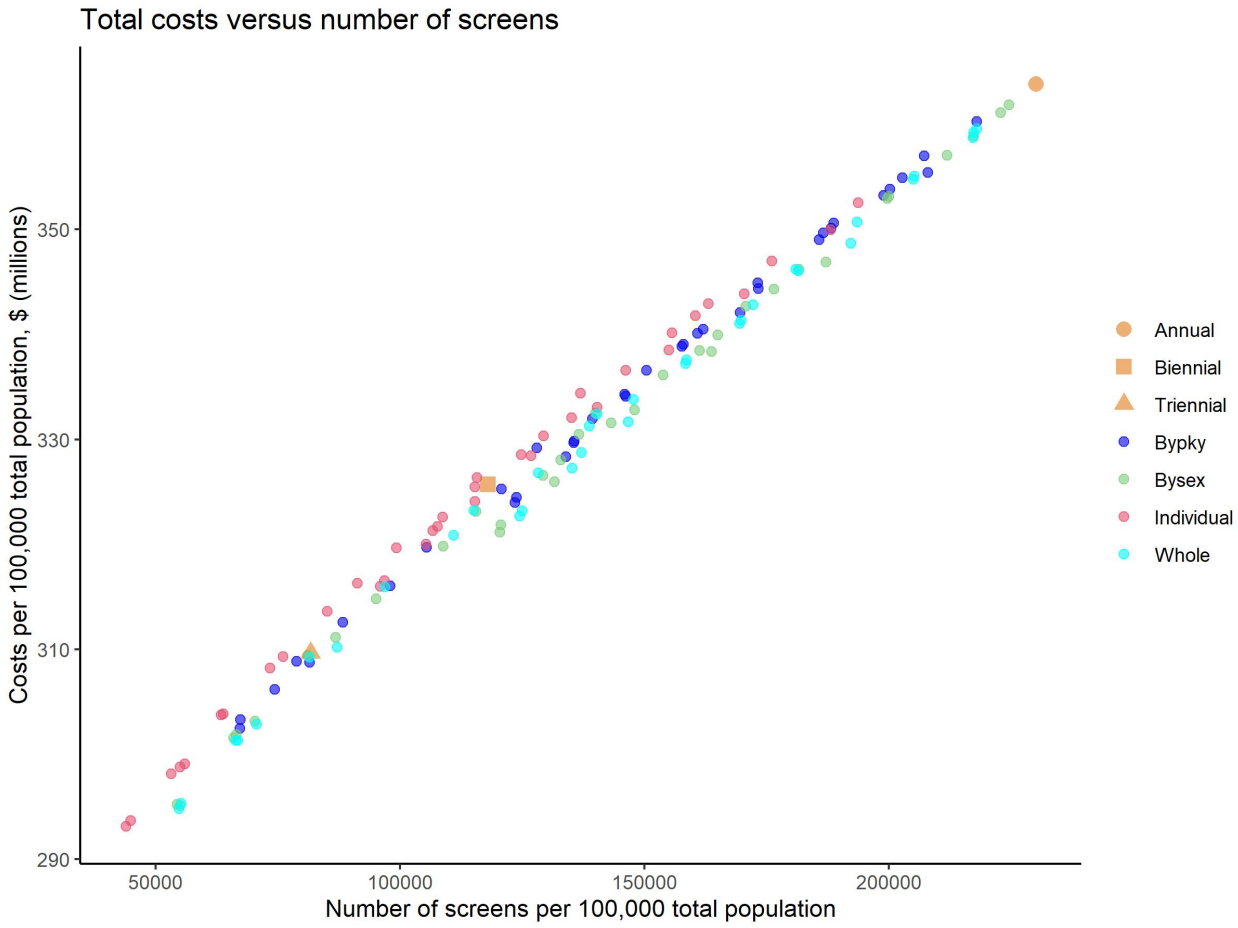
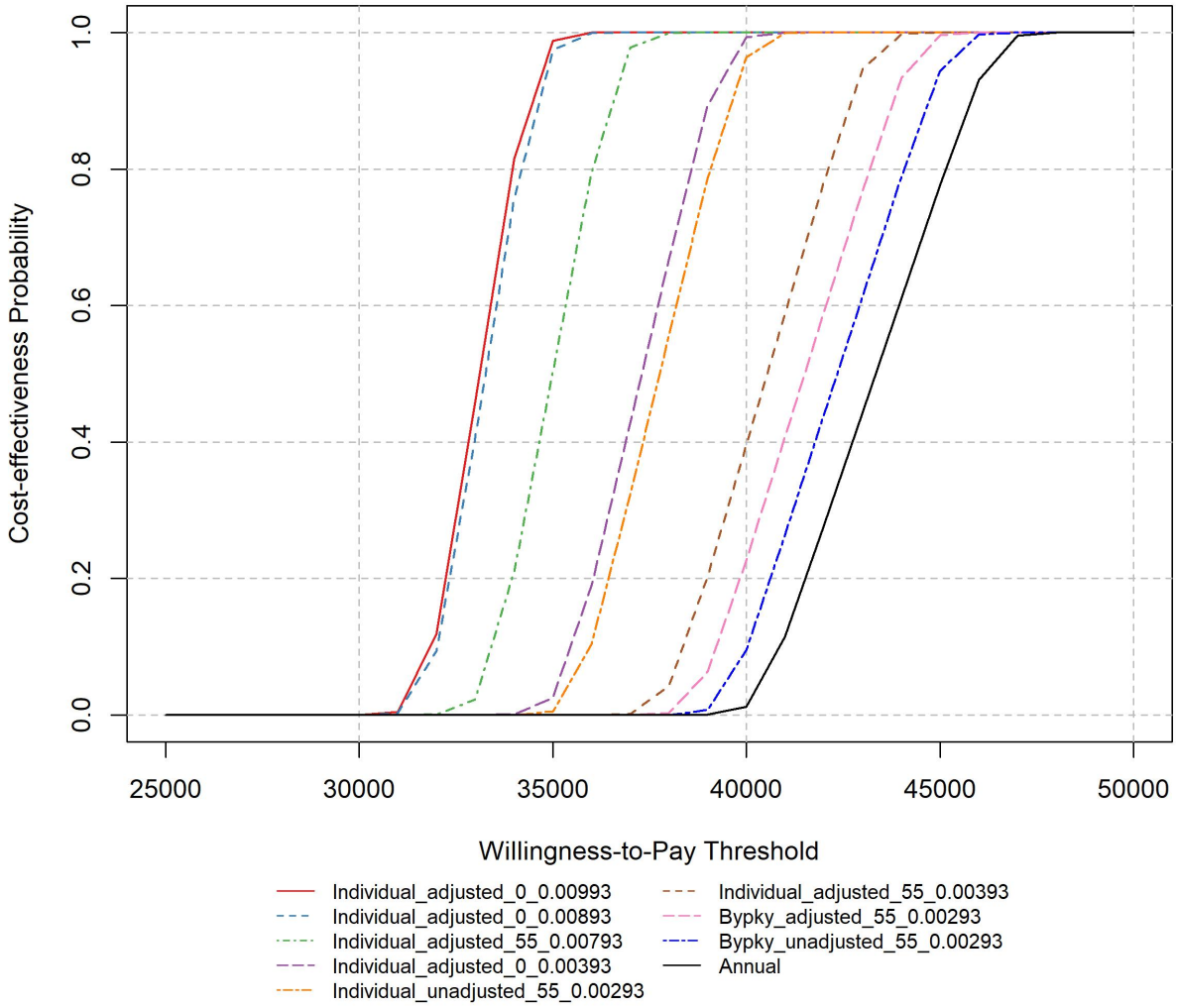


Figure D.2. Cost-effectiveness acceptability curves for the 9 dominant strategies in the base-case analysis. The cost effectiveness of each strategy is calculated relative to no screening



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