

# The Benefits and Harms of Lung Cancer Screening in Individuals With Comorbidities



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## ABSTRACT

**Introduction:** Individuals with a history of smoking and a high risk of lung cancer often have a high prevalence of smoking-related comorbidities. The presence of these comorbidities might alter the benefit-to-harm ratio of lung cancer screening by influencing the risk of complications, quality of life, and competing risks of death. Nevertheless, individuals with chronic diseases are underrepresented in screening clinical trials. In this study, we use microsimulation modeling to determine the impact of chronic diseases on lung cancer benefits and harms.

**Methods:** We extended a validated lung cancer screening microsimulation model that comprehensively recapitulates an individual's lung cancer development, progression, detection, follow-up, treatment, and survival. We parameterized the model to reflect the impact of chronic diseases on complications from invasive testing, quality of life, and mortality in individuals in five-year age categories between the ages of 50 and 80 years. Outcomes included life-years (LY) gained per 100,000 in patients with chronic obstructive pulmonary disease, diabetes mellitus, heart disease, and history of stroke compared with screening-eligible individuals without comorbidities.

**Results:** Among individuals between the ages of 50 and 54 years, we found that the presence of a comorbidity altered the LY gained from screening per 100,000 individuals depending on the comorbidity: 4296 LY with no comorbidities; 3462 LY, 3260 LY, 3031 LY, and 3257 LY with chronic obstructive pulmonary disease, heart disease, diabetes mellitus, and stroke, respectively. We observed greater reductions in LY gained in individuals with two comorbidities; we observed similar patterns for individuals

between the ages of 55 and 59 years, 60 and 64 years, 65 and 69 years, 70 and 74 years, and 75 and 80 years.

**Conclusions:** Comorbidities reduce LY gained from screening per 100,000 compared with no comorbidities, and our results can be used by clinicians when discussing the benefits and harms of screening in their patients with comorbidities.

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**Keywords:** Microsimulation modeling; Lung cancer screening; Comorbidity; Decision analytic model

## Introduction

Individuals in the United States between the ages of 50 and 80 years who have smoked at least 20 pack-years and currently smoke or have quit within the past 15

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years are eligible for lung cancer screening (LCS). The U.S. Preventive Services Task Force (USPSTF) recommends LCS for such high-risk individuals; these recommendations are supported by the results of multiple randomized controlled trials (RCTs) including the National Lung Screening Trial (NLST).<sup>1–3</sup> The NLST was the first RCT to reveal a 20% reduction in lung cancer mortality associated with low-dose computed tomography screening.<sup>2,3</sup> Nevertheless, it is important to note that the study population of the NLST and most RCTs consisted of relatively healthy participants, which may not be representative of the general population of current and former smokers.<sup>4</sup> Patients with comorbidities were substantially underrepresented in the NLST. A comparison of screening-eligible smokers from a population-based study versus NLST participants found that the former group was older, had a higher prevalence of comorbidities, and had a shorter life expectancy.<sup>5</sup> In addition, modeling studies evaluating the effectiveness of low-dose computed tomography did not fully consider the impact of comorbidities on the benefits and harms of screening. Therefore, it is unclear whether caution should be exercised when generalizing the results of NLST to the population of screening-eligible smokers, especially those with comorbidities.

Individuals at high risk of lung cancer often have a high prevalence of smoking-related comorbidities.<sup>5</sup> Among the most common is chronic obstructive pulmonary disease (COPD), which co-occurs in approximately 35% of screening-eligible individuals.<sup>6–8</sup> In addition, cardiovascular disease (CVD), including both ischemic heart disease and congestive heart failure, frequently co-occur, affecting approximately 30% of screening-eligible individuals.<sup>4</sup> Other comorbidities such as stroke (11% prevalence) and diabetes mellitus (DM, approximately 25% prevalence) also frequently co-occur.<sup>5</sup> These comorbidities may increase the risk of complications related to the workup of suspicious nodules and lead to decreased quality of life and a limited life expectancy, substantially altering the harm-benefit ratio of LCS. The high burden of comorbidities among individuals who smoke may have contributed to the cautious adoption of LCS, despite the evidence of its effectiveness.<sup>9</sup> A study evaluating LCS implementation in eight Veterans Administration hospitals found that physicians excluded many USPSTF-eligible individuals from screening due to their comorbidities.<sup>10</sup>

At present, clinicians have no guidance to determine whether individuals with comorbidities will benefit from LCS. There has been an urgent call by the American Thoracic Society and others for research that can help direct clinical decision-making with patients who may experience different harms and benefits from LCS due to coexisting chronic illness.<sup>11,12</sup> Exploring the nuanced

relationship between lung cancer risk and screening and diagnostic and treatment-related harms that may be worsened by chronic disease and risk of death from competing causes is crucial in determining the indications for LCS. In this study, we use simulation modeling to determine the benefits and harms of individuals eligible for LCS while considering comorbidities. Simulation modeling is a comparative effectiveness technique that has been successfully used to extrapolate findings to unstudied groups, offering a complementary approach to RCTs. Modeling has been used to inform national guidelines for breast, colorectal, and lung cancer screening.<sup>13–16</sup>

## Methods

### Simulation Model Overview

We developed our LCS simulation model by creating an improved version of a National Cancer Institute-sponsored state-transition microsimulation model that comprehensively simulates a patient's lung cancer development, progression, detection, follow-up, treatment, and survival.<sup>17–21</sup> The model was used in the development of two rounds of the USPSTF's LCS recommendations.<sup>13,22</sup> We developed the model using a rigorous, object-oriented design that generates the life histories of simulated patients. The model initially populates with disease-free individuals who then go through different health states according to monthly transition probabilities. In each monthly cycle, an individual may develop lung cancer, have an existing cancer grow, or develop metastases.<sup>23</sup> The model has been extensively calibrated and validated.<sup>24,25</sup> Although the model was comprehensive, it did not incorporate details on the simulated patient's comorbidities and the outcomes of follow-up procedures and lung cancer treatments based on patients' underlying health conditions. For this study, we have expanded the model to estimate the outcomes of LCS based on patients' comorbidities. The study was determined to be exempt human research as defined by DHHS regulations by the Institutional Review Board of Icahn School of Medicine at Mount Sinai (HS-19-01319).

### Model Inputs for Patients With Comorbidities

We comprehensively reviewed the literature and conducted primary analyses of a large cancer screening data set to assess factors unique to patients with comorbidities who are eligible for LCS. The newly parameterized model reflects changes to mortality (from competing risks), complications from workup, and quality of life utilities among these individuals. Parameters and data sources are listed in [Table 1](#),<sup>26–31</sup> [Supplementary Table 1](#), and [Supplementary Table 2](#).

**Table 1.** Key Input Parameters for Developing a Microsimulation Model of Lung Cancer Screening in Patients With Comorbidities

Model Parameter	Definition	Value	Sources
Complications from Lung Cancer Screening	Probability of complications from lung cancer screening	Supplementary Table 1	Previous work using PLCO <sup>26</sup>
Mortality from Non-Lung Cancer Causes	Death rates for non-lung cancer causes by age and comorbidity	Supplementary Table 2	Secondary data, NHIS
		Comorbidity	Utility
Quality of Life for Patients With Comorbidities	Expected quality of life by comorbidity	Stroke	-0.051 <sup>27-31</sup>
		DM	-0.044
		COPD	-0.038
		CVD	-0.0235

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; NHIS, National Health Interview Survey; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

### Probability of Complications Due to Comorbidities

To estimate the probability of complications from LCS diagnostic evaluation, we used data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) to identify participants with baseline questionnaire information that included risk factors and health history.<sup>26</sup> We identified 3032 participants above 50 years old with at least a 20 pack-year smoking history and who had one or more diagnostic procedures, defined as surgical biopsy (including thoracotomy, thoracoscopy, and resection), needle biopsy (including thoracentesis), bronchoscopy (with or without biopsy), mediastinoscopy, and “other” procedure. Our primary outcomes were complications stratified by severity (major, intermediate, and minor) and comorbidity and defined as those that occurred within 14 days of needle biopsy and bronchoscopy and within 60 days of mediastinoscopy and surgical biopsy (see the definitions of severity in Supplementary Table 3).

### Chronic Disease Mortality

To estimate chronic disease-attributed mortality, we conducted analyses of the National Health Interview Survey (NHIS), which is a series of annual cross-sectional national surveys that provide information on the health of the noninstitutionalized population of the United States. The sample design uses a multistage area probability design that adjusts for nonresponse and further allows for a nationally representative sampling of households and individuals, including traditionally underrepresented groups. We used the publicly available NHIS Linked Mortality File, which provides users with information from the National Death Index (NDI) for eligible NHIS respondents. We used self-reported age, sex, comorbidities, and smoking history for NHIS files from 1998 to 2018 and removed lung cancer deaths. We estimated the baseline hazard and

hazard ratios using age, sex, self-reported comorbidities, and smoking history.

### Quality-Adjusted Life Expectancy

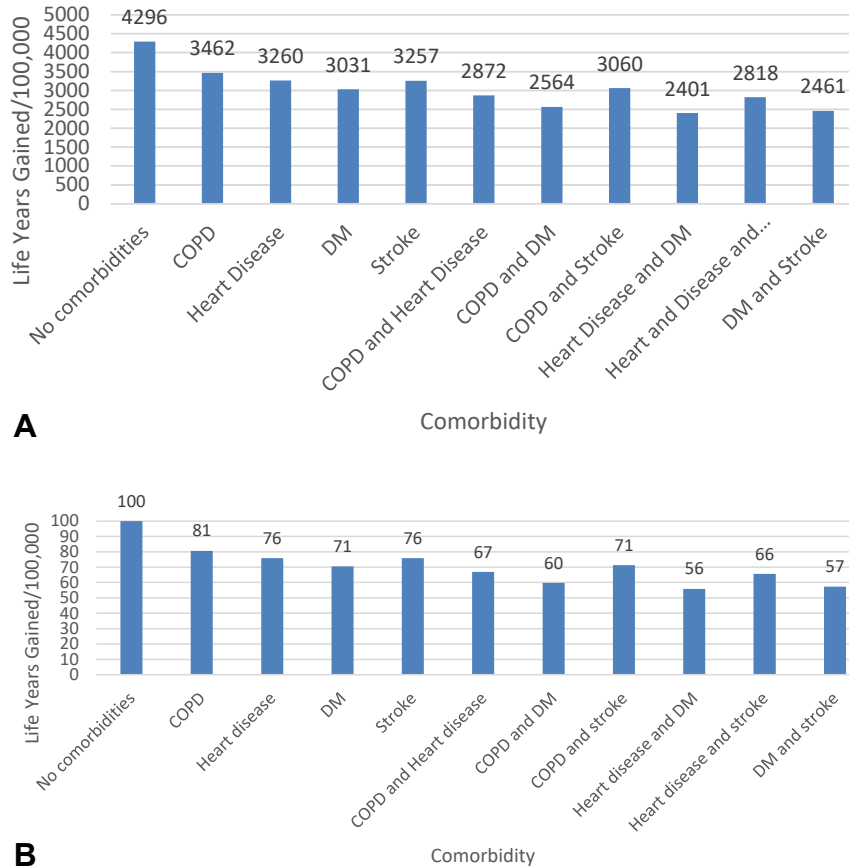
We accounted for quality of life affected by comorbidities by comprehensively reviewing the literature to derive the negative impact of comorbidities with estimated utility values based on the Eq-5D administered in the National Health Measurement Study.<sup>27-31</sup>

### Population

The model was populated with 1 million individual men and women in the following six age categories: 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74, and 75 to 80 years of age. We segmented age into five-year increments, as this interval is suitable for assessing the influence of chronic diseases on quality of life and life expectancy within the screening age range of 50 to 80 years, consistent with the LCS recommendations of the USPSTF. Smoking histories for each person were simulated by the CISNET Smoking History Generator, which was developed to provide stochastic simulation of smoking history specific to age, birth cohort, and sex (more information may be found at <https://cisnet.cancer.gov/lung>).<sup>32-35</sup> Standardized inputs from the SHG include rate of smoking initiation, smoking intensity, and rate of smoking cessation.

### Outcomes

The primary analysis focused on the 2011 USPSTF eligibility criteria of 20 pack-year smoking history and annual screening between the ages 50 and 80 years. The model was used to estimate the benefits and harms of screening in patients with comorbidities who received screening versus individuals without comorbidities. Simulated outcomes included life-years (LY) and quality-adjusted life years (QALY) gained per



**Figure 1.** (A) Life-years gained per 100,000 screened in individuals 50 to 54 years of age. (B) Relative life-years gained per 100,000 from screening in individuals 50 to 54 years of age. DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

100,000 individuals to compare patients with comorbidities who received screening to individuals without comorbidities who received screening. We also evaluated lung cancer deaths averted per 100,000 individuals and lifetime cumulative lung cancer mortality reduction if annual screening is initiated for individuals in a specific age range. Harms included the number of complications, including major, intermediate, and minor per 100,000 screened individuals. We also evaluated the number of biopsies. We simulated patients up to age 100 years with lone comorbidities and the presence of two comorbidities.

## Results

Figure 1A summarizes the life-years gained per 100,000 individuals based on presence of comorbidity relative to individuals without comorbidities; complete estimates for all age categories can be found in the Supplement. For example, per 100,000 individuals without comorbidities screened between the ages of 50 and 54 years, 4296 LY were gained, compared with individuals with COPD (3462 LY-gained), heart disease

(3260 LY-gained), DM (3031 LY-gained), stroke (3257 LY-gained), COPD and heart disease (2872 LY-gained), COPD and DM (2564 LY-gained), COPD and stroke (3060 LY-gained), heart disease and DM (2401 LY-gained), heart disease and stroke (2818 LY-gained), and DM and stroke (2461 LY-gained). In [Supplementary Figures 1 and 2](#), we summarize the effects of screening on LY-gained in all age group categories. Among individuals in the highest age category (75–80 yo), we found that screening led to 1237 LY gained per 100K screened, compared with individuals with COPD (1006 LY-gained), heart disease (957 LY-gained), DM (898 LY-gained), and stroke (941 LY-gained). We found a similar pattern of effect of comorbidities on LY-gained from screening in each age group; with screening leading to the highest LY-gained among individuals without comorbidities and declining LY-gained among individuals with comorbidities in each age group.

In [Figure 1B](#), we summarized these results as proportions relative to individuals without comorbidities. We found that compared with individuals without comorbidities, the presence of one or more comorbidities led to relative LY gained from screening ranging from 56% to

**Table 2. Lung Cancer Mortality Reduction in Individuals With One Comorbidity**

Age (y)	No Comorbidities (%)	COPD (%)	Heart Disease (%)	DM (%)	Stroke (%)
50-54	9.98	10.03	10.07	10.09	10.07
55-59	9.34	9.61	9.61	9.70	9.61
60-65	9.13	9.18	9.29	9.34	9.28
65-69	8.54	8.70	8.75	8.82	8.75
70-74	6.98	7.11	7.09	7.19	7.09
75-80	5.33	5.51	5.41	5.42	5.54

DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

81%. In individuals between the ages of 75 and 80, LY gained relative to individuals with no comorbidities ranged from 28% to 81% (Supplementary Figs. 1 and 2), with similar ranges for other age groups. The estimated number of QALY gained per 100,000 due to screening by presence of one or two comorbidities followed the general pattern of LY gained (Supplementary Figs. 3 and 4).

### Lung Cancer Deaths Averted and Lung Cancer Mortality Reduction

The estimated number of lung cancer deaths averted (Supplementary Table 4) per 100,000 screened individuals between the ages of 50 and 54 years was 399 (3465 and 3066 without and with screening, respectively) for individuals with no comorbidities and ranged from 334 (DM—3255 and 2921 without and with screening, respectively) to 365 (COPD—3330 and 2965 without and with screening, respectively) per 100,000 screened individuals with one comorbidity. This corresponded to a lung cancer mortality reduction ranging from 10.0% to 10.1% for individuals with one comorbidity and 10.0% for individuals with no comorbidities (Table 2). We found declining numbers of lung cancer deaths averted with increasing age, corresponding to declining lung cancer mortality reduction. For individuals between the ages of 75 and 80 years, there were 250 lung cancer deaths averted for those with no comorbidities and ranged from 207 (DM) to 232 (COPD) per 100,000 screened individuals with one comorbidity (Supplementary Table 4).

The lung cancer mortality reduction for individuals between the ages of 75 and 80 years was 5.3% with no comorbidities and ranged from 5.4% to 5.1% for individuals with one comorbidity. In the presence of two comorbidities (Table 3), lung cancer mortality reductions similarly declined with increasing age.

### Complications From Screening

We simulated the numbers of biopsies performed per 100,000 screened individuals (Supplementary Table 5). These analyses revealed that the presence of comorbidities led to a decrease in the number of biopsies performed, with larger decreases in the presence of two comorbidities due to a shorter life expectancy and fewer screenings and evaluations. Among individuals between the ages of 50 and 54 years, there were 862, 852, and 841 biopsies per 100,000 screened individuals in the setting of no comorbidities, COPD, and COPD and heart disease, respectively. Among individuals between the ages of 75 and 80 years, there were 248, 248, and 237 biopsies per 100,000 screened individuals in the setting of no comorbidities, COPD, and COPD and heart disease, respectively. Increasing age led to a decrease in the number of biopsies performed across all comorbidities. We used our microsimulation to estimate the occurrence of major complications per 100,000 screened individuals (Table 4). In individuals between the ages of 50 and 54 years without comorbidities, there were 44.7 major complications, and in the presence of a lone comorbidity, there were 29.8 to 45.6 major complications. In the presence of two comorbidities, there were

**Table 3. Lung Cancer Mortality Reduction in Individuals With Two Comorbidities**

Age (y)	COPD and Heart Disease (%)	COPD and DM (%)	COPD and Stroke (%)	Heart Disease and DM (%)	Heart Disease and Stroke (%)	DM and Stroke (%)
50-54	10.19	10.26	10.15	10.25	10.19	10.25
55-59	9.76	9.77	9.74	9.78	9.75	9.74
60-65	9.27	9.27	9.25	9.39	9.40	9.43
65-69	8.78	8.84	8.79	8.86	8.82	8.86
70-74	7.18	7.16	7.17	7.18	7.21	7.17
75-80	5.63	5.51	5.64	5.63	5.50	5.35

DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

Table 4. Major Complications per 100,000

Age (y)	No Comorbidities		Heart Disease		COPD and Heart Disease		COPD and DM		COPD and Stroke		Heart Disease and DM		Heart Disease and Stroke		DM and Stroke	
	No	Comorbidities	COPD	Heart Disease	DM	Stroke	COPD and Heart Disease	DM	COPD and Stroke	Stroke	Heart Disease and DM	DM	Heart Disease and Stroke	Stroke	DM and Stroke	Stroke
50-54	44.7 (<0.1%)	45.0 (<0.1%)	45.6 (<0.1%)	29.8 (<0.1%)	29.8 (<0.1%)	45.3 (<0.1%)	46.0 (<0.1%)	46.6 (<0.1%)	45.7 (<0.1%)	44.1 (<0.1%)	43.8 (<0.1%)	45.5 (<0.1%)	44.1 (<0.1%)	45.7 (<0.1%)	43.5 (<0.1%)	45.4 (<0.1%)
55-59	43.0 (<0.1%)	43.1 (<0.1%)	43.8 (<0.1%)	28.7 (<0.1%)	28.7 (<0.1%)	43.6 (<0.1%)	44.2 (<0.1%)	44.9 (<0.1%)	44.1 (<0.1%)	44.1 (<0.1%)	43.8 (<0.1%)	43.8 (<0.1%)	44.1 (<0.1%)	44.1 (<0.1%)	43.5 (<0.1%)	43.5 (<0.1%)
60-65	32.4 (<0.1%)	32.7 (<0.1%)	33.5 (<0.1%)	21.6 (<0.1%)	21.6 (<0.1%)	33.1 (<0.1%)	33.8 (<0.1%)	34.2 (<0.1%)	33.4 (<0.1%)	33.4 (<0.1%)	33.2 (<0.1%)	33.2 (<0.1%)	33.4 (<0.1%)	33.4 (<0.1%)	33.2 (<0.1%)	33.2 (<0.1%)
65-69	29.4 (<0.1%)	29.9 (<0.1%)	30.8 (<0.1%)	19.5 (<0.1%)	19.5 (<0.1%)	30.0 (<0.1%)	31.2 (<0.1%)	31.6 (<0.1%)	30.6 (<0.1%)	30.6 (<0.1%)	30.3 (<0.1%)	30.3 (<0.1%)	30.6 (<0.1%)	30.6 (<0.1%)	30.5 (<0.1%)	30.5 (<0.1%)
70-74	20.4 (<0.1%)	20.8 (<0.1%)	21.3 (<0.1%)	13.4 (<0.1%)	13.4 (<0.1%)	20.7 (<0.1%)	21.7 (<0.1%)	22.0 (<0.1%)	21.1 (<0.1%)	21.1 (<0.1%)	20.9 (<0.1%)	20.9 (<0.1%)	21.1 (<0.1%)	21.1 (<0.1%)	21.2 (<0.1%)	21.2 (<0.1%)
75-80	11.2 (<0.1%)	11.6 (<0.1%)	11.6 (<0.1%)	7.5 (<0.1%)	7.5 (<0.1%)	11.7 (<0.1%)	12.2 (<0.1%)	12.5 (<0.1%)	11.4 (<0.1%)	11.4 (<0.1%)	11.6 (<0.1%)	11.6 (<0.1%)	11.8 (<0.1%)	11.8 (<0.1%)	12.0 (<0.1%)	12.0 (<0.1%)

DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

45.4 to 46.6 major complications per 100,000 screened individuals. In individuals between the ages of 75 and 80 years, there were 11.2 major complications per 100,000 screened individuals, and in the presence of a lone comorbidity, there were 7.5 to 11.7 major complications per 100,000 screened individuals. In the presence of two comorbidities, there were 11.4 to 12.5 major complications per 100,000 screened individuals.

Across all age ranges, the presence of comorbidities with the exception of DM led to increased major complications. This pattern was also observed in estimated intermediate and minor complications (Supplementary Tables 6 and 7).

## Discussion

In this study, we expanded an established LCS microsimulation model to evaluate the impact of the presence of diabetes, stroke, COPD, and CVD on LCS benefits and harms. We found that in individuals with one and two comorbidities, there was a decrease in projected LY gained and a larger decrease in QALY gained per 100,000 screened compared with individuals with no comorbidity with little impact on complications from screening. The relative decrease in LY and QALY gained per screening was constant across age groups. We also found that the presence of comorbidities led to a reduced estimate of lung cancer deaths averted as the presence of comorbidities led to a shortened life expectancy. Nevertheless, this did not translate into attenuated lung cancer mortality reduction, which is a ratio of lung cancer deaths averted divided by total lung cancer deaths, as comorbidities affected both parts of this ratio. Our findings suggest that the presence of comorbidities diminishes LCS benefit in individuals with comorbidities without affecting harms.

The potential impact of comorbidities on LCS benefit and harm gained substantial attention in large part because of recommendations from the USPSTF, which advised that LCS should be discontinued if a person develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.<sup>1</sup> The presence of comorbidities leading to excessive harm was further explicated in the Medicare policy decision, in which individuals should be counseled on the “the impact of comorbidities.”<sup>36</sup> These policy decisions were in advance of supporting evidence; our study is among the first to use microsimulation modeling to determine the population impact of comorbidities on LCS benefit and harm.

Systematic reviews and meta-analyses have confirmed the higher prevalence of comorbidities in the general population compared with clinical trials.<sup>4,37</sup> The underrepresentation of individuals with comorbidities is

true of LCS trials as well.<sup>38–40</sup> Nevertheless, studies assessing the impact of these comorbidities on LCS have been limited to the complication rate. A secondary analysis of data from the NLST found that COPD increased the risk of complications from an invasive evaluation; however, a real-world investigation of Veterans found that comorbidities (with the exception of dementia) were not associated with an increase in complications.<sup>41,42</sup> In our study, we found that the presence of chronic diseases on competing risk of mortality had the greatest impact on LCS outcomes. There is a growing recognition of the importance of accounting for competing risks of death from chronic diseases in individuals with cancer; competing risks can affect cancer mortality by reducing the probability of dying from cancer as individuals age and become more susceptible to other causes of death.<sup>43</sup> This is an important factor despite the aggressiveness of cancer, such as in lung cancer. In one institution-based study of early stage lung cancer, the cumulative incidence of non-cancer death was higher than cancer death in the 2.5 years after surgery among people more than 65 years of age.<sup>44</sup> In our study, we found that LY gained from screening was diminished by 20% to 30% with one comorbidity and by 40% to 45% with two comorbidities; the presence of DM led to the greatest reduction in LY and QALY gains. Multiple population-based studies have revealed that DM increases the risk of all-cause mortality and other disease-specific mortality, such as CVD.<sup>45,46</sup>

There are limitations to our study. We determined the presence of comorbidity in the PLCO using self-report and had limited ability to determine severity of disease. PLCO is also an older LCS trial and, as such, reflects a slightly different diagnostic landscape than the advances in fine-needle biopsy and minimally invasive techniques. Nevertheless, the use of this data set allowed us to include individuals with at least a 20 pack-year smoking history which other cancer screening data sets did not include. In addition, the content of NHIS surveys changed over time, so we were limited to using data sets after the year 1997 to be able to appropriately estimate the impact of our chronic diseases of interest. Nevertheless, the use of NHIS linked to mortality data enabled us to have a rich data source with cause of death. Furthermore, the NHIS establishes the presence of chronic diseases by self-report, which may have led to underreporting of certain diseases such as COPD.<sup>47</sup> Future modeling work will assess the impact of the presence of three or more comorbidities in this population and model the potential benefits and harms of the identification of not only lung cancer but also the radiographic presence of emphysema and coronary artery calcifications.

In summary, we used a simulation model to evaluate the LY and QALY gains from screening for patients with

comorbidities who are eligible for LCS. We found that the presence of comorbidities decreased LY and QALY compared with individuals with no comorbidities without affecting harms such as complications from invasive diagnostic testing. We also found that this loss was primarily due to competing risk of death from chronic disease. This was especially true for individuals with two comorbidities. Our results help to contextualize the benefits of screening for patients who are underrepresented in clinical trials, which favor the healthy and those without chronic disease. Nevertheless, additional research is needed to understand how these findings may be translated in clinical practice, as LY and QALY are chiefly used to determine health care policies.

## CRediT Authorship Contribution Statement

**Minal S. Kale:** Had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Concept and design; Acquisition, analysis, or interpretation of data; Drafting of the manuscript; Statistical analysis; Funding; Supervision.

**Keith Sigel:** Acquisition, analysis, or interpretation of data; Critical revision of the manuscript for important intellectual content.

**Arushi Arora:** Acquisition, analysis, or interpretation of data; Statistical analysis.

**Bart S. Ferket:** Acquisition, analysis, or interpretation of data; Critical revision of the manuscript for important intellectual content.

**Juan Wisnivesky:** Acquisition, analysis, or interpretation of data; Critical revision of the manuscript for important intellectual content.

**Chung Yin Kong:** Concept and design; Acquisition, analysis, or interpretation of data; Critical revision of the manuscript for important intellectual content; Statistical analysis; Supervision.

## Disclosure

Dr. Wisnivesky has received consulting honorarium from Sanofi, PPD, and Banook and research grants from Sanofi, Regeneron, Axella, and Arnold Consultants. The remaining authors declare no conflict of interest.

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## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at [www.jtocrr.org](http://www.jtocrr.org) and at <https://doi.org/10.1016/j.jtocrr.2024.100635>.

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