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Incorporating Coexisting Chronic Illness into Decisions about Patient Selection for Lung Cancer Screening

An Official American Thoracic Society Research Statement

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Background: Lung cancer screening (LCS) has the potential to reduce the risk of lung cancer death in healthy individuals, but the impact of coexisting chronic illnesses on LCS outcomes has not been well defined. Consideration of the complex relationship between baseline risk of lung cancer, treatment-related harms, and risk of death from competing causes is crucial in determining the balance of benefits and harms of LCS.

Objectives: To summarize evidence, identify knowledge and research gaps, prioritize topics, and propose methods for future research on how best to incorporate comorbidities in making decisions regarding LCS.

Methods: A multidisciplinary group of international clinicians and researchers reviewed available data on the effects of comorbidities on LCS outcomes, focusing on the juxtaposition of lung cancer risk and competing risks of death, consideration of benefits and risks in patients with chronic obstructive pulmonary disease, communication of risk, and treatment of screen-detected lung cancer.

Results: This statement identifies gaps in knowledge regarding how comorbidities and competing causes of death impact outcomes in LCS, and we have developed questions to help guide future research efforts to better inform patient selection, education, and implementation of LCS.

Conclusions: There is an urgent need for further research that can help guide clinical decision-making with patients who may not benefit from LCS owing to coexisting chronic illness. This statement establishes a research framework to address essential questions regarding how to incorporate and communicate risks of comorbidities into patient selection and decisions regarding LCS.

Keywords: lung cancer screening; comorbidities; communication of risk

Contents

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Overview

An efficacious screening test must identify disease with high prevalence, mortality, and cure rate when detected at an early stage in individuals who are healthy enough to undergo effective treatment. Lung cancer screening (LCS) with annual low-dose computed tomography (LDCT) satisfies these criteria, and if implemented correctly, it may be the single intervention, other than quitting smoking, with the largest effect on decreasing cancer deaths in our lifetime. The NLST (National Lung Screening Trial), however, which provides the evidence for LCS, suffers from the "healthy volunteer effect." This phenomenon, in which participants are better educated, younger, and have less comorbid disease than the general population that would otherwise qualify for LCS, is commonly seen in screening trials and draws concerns about the generalizability of the NLST, especially in groups underrepresented in the trial. Smoking, the primary risk factor for lung cancer, also increases the risk for other respiratory and cardiovascular diseases (CVDs), which, when severe enough, have substantial implications for treatment decisions and outcomes for both lung cancer and chronic disease. High risk of lung cancer is associated with greater risk of death not related to lung cancer, harms from procedures, and diminished ability to treat a screen-detected cancer, undermining the benefits of screening. A significant challenge in LCS implementation is how to incorporate comorbid disease of varying severity into decisions regarding LCS to improve the selection of those at higher risk for complications and simultaneously improve the harm-to-benefit ratio of screening.

This statement proposes a research agenda to apprise both investigators and funding agencies to generate high-priority, high-quality research surrounding the incorporation of severity and number of comorbidities in decisions around LDCT screening. Topics were identified including *1*) juxtaposing lung cancer risk and competing risks of death; *2*) chronic obstructive pulmonary disease (COPD), lung cancer risk, and potential harms from screening; *3*) risk communication; and *4*) treatment of screen-detected cancer. For each of these overarching topics, the existing evidence is summarized, and research gaps and questions to be answered are identified.

Key Conclusions and Recommendations

Juxtaposing lung cancer risk and competing risk of death.

- Better selection of those at high risk for lung cancer may improve the harm-to-benefit ratio of screening; however, benefits and harms of LCS may not be linearly related to risk of developing lung cancer.
- The complex interplay between baseline risk of developing lung cancer, treatment-related harms, and competing causes of death substantially affects the balance of harms and benefits of LCS.
- Research is needed to identify the optimal threshold where the benefits of reducing lung cancer death (LCD) outweigh the risk of dying of a competing cause and serve to prolong survival.

COPD, lung cancer risk, and potential harms of LDCT screening.

- Although individuals with COPD have a higher risk than smokers without COPD of developing lung cancer, the presence of advanced COPD may pose a significant risk for harms of LCS and downstream evaluation and treatment of screen-detected nodules.
- The benefit of screening those with advanced-stage COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] classes 3 and 4) is uncertain, and how best to risk stratify these patients using functional status information should be an area of research.

Risk communication.

- Providers vary in their comfort level regarding advising patients meeting eligibility criteria not to undergo screening owing to poor overall health or limited life expectancy.
- Message framing is critical, but how best to do this remains unclear.
- Research is needed to identify how best to support providers through training, education, and decision support tools.

Treatment of screen-detected lung cancer.

- There are currently no data on whether screening decreases lung cancer mortality among patients who are unable or unwilling to undergo anatomic resection for a screen-detected cancer.
- There is controversy and confusion regarding who should be offered screening, and future research is needed with the aim of incorporating the balance of risk of LCD, competing causes of death, morbidity, mortality, and efficacy of treatment approaches in the face of comorbidities.

Introduction

The NLST demonstrated that screening with LDCT reduced LCDs and overall mortality (1). However, as in many clinical trials, participants were healthier than the base population. When compared with a general population of individuals eligible for LCS in the United States, the NLST participants were younger, healthier, better educated, less likely to be racial minorities, and more likely to be former smokers (2). These sociodemographic differences raise questions about the generalizability of the NLST, especially as it relates to those underrepresented in the trial. It also presents challenges for clinicians deciding which patients are appropriate candidates for LCS, because there is limited evidence from secondary analyses of NLST data to guide decision-making about which patients may be too sick owing to competing comorbidities to benefit from screening (3).

Patient selection for LCS is complex, because factors that increase the risk of developing lung cancer (e.g., smoking) also correlate with risk of developing other diseases associated with high morbidity and mortality (e.g., COPD, CVD, other cancers). Competing risk is defined as the risk that a substitute event (e.g., cardiovascular death) interferes with the likelihood that an individual will experience the disease-specific outcome of interest (e.g., LCD) (4). As risk of lung cancer increases, so does competing risk of death and harms of diagnostic evaluation and treatment of screen-detected lung cancer, potentially decreasing the net benefit of LCS (Figures 1A and 1B). How to determine the number, severity, and combination of comorbid conditions in which competing causes of death or reduced ability to tolerate diagnostic procedures and cancer treatment would diminish the benefit of LCS is unclear. Furthermore, communication and decision tools regarding trade-offs of LCS in the face of comorbidities are undeveloped.

To advance the field, the American Thoracic Society (ATS) convened a multidisciplinary panel to summarize the available data surrounding the impact of comorbid conditions as it relates to LCS. In this research statement, we aimed to identify and prioritize gaps in knowledge to outline and help guide the formation of research efforts in these areas to better inform patient selection for and education about LCS.

Methods

The project was sponsored by the Thoracic Oncology Assembly and approved by the ATS Project Review Subcommittee. The multidisciplinary, international participants (pulmonologists, thoracic surgeons, internists, nurse practitioners, and epidemiologists) were chosen by the project chairs (M.P.R., N.T.T., and R.S.W.) because of their expertise in all aspects of LCS, evaluation of comorbidities, and lung cancer treatment outcomes. Representatives of other professional societies, including the American College of Chest Physicians, Society of Thoracic Surgery, International Association for the Study of Lung Cancer, and American College of Physicians, were invited to ensure a diverse representation. Conflicts of interest were disclosed and managed according to the policies and procedures of the ATS. The chairs identified several topics for discussion that were vetted before the in-person meeting, and relevant articles were distributed to participants. Participants selected to be speakers provided input on the agenda.

The group met at the ATS International Conference in Washington, DC, in May 2017, with main foci of identifying the gaps in knowledge about how comorbid conditions impact outcomes in LCS and identifying and prioritizing key research questions that will lead to optimized screening in patients with comorbid conditions. The in-person meeting included presentations reviewing existing data on the following six key topics:

1. How do screen-eligible U.S. individuals differ from NLST participants?
2. What is the impact of comorbidities on cancer survival?
3. How can prediction of non–lung cancer deaths in persons screened for potential lung cancer be improved?
4. What are the special considerations for patients with COPD that serve as a marker for increased risk of lung cancer, increased risk of death from competing causes, and decreased ability to tolerate surgery for screen-detected cancers?
5. What is the outcome of surgery for stage I non–small cell lung cancer (NSCLC) in smokers with advanced COPD or other serious comorbidities?
6. What is the role of stereotactic body radiation therapy (SBRT) as an alternative treatment in early-stage NSCLC detected through LCS?

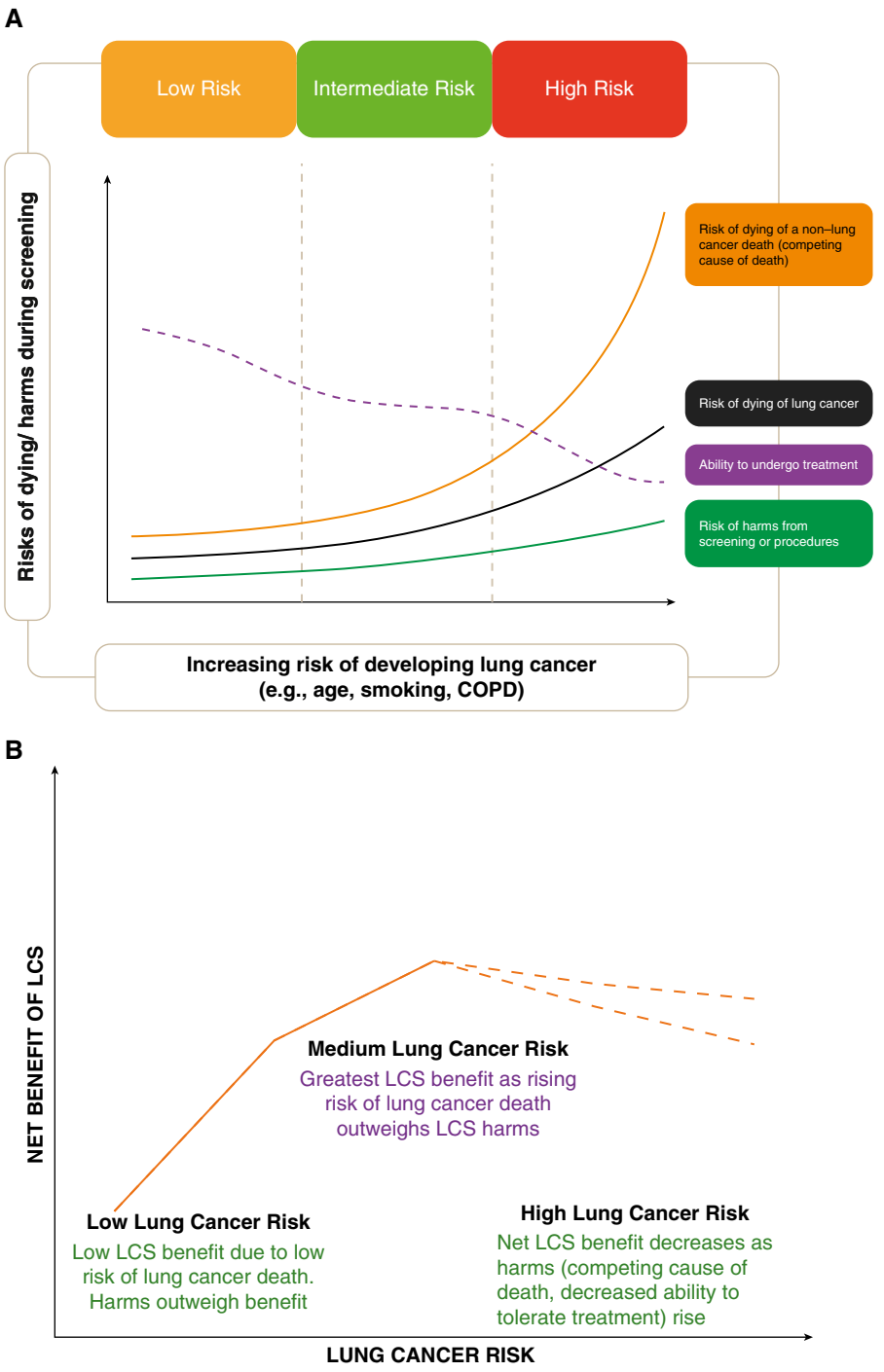

Figure 1. (*A*) Hypothetical schema of the risk of developing lung cancer versus the ability to undergo treatment, risk of death from competing causes, and risk of harms of procedures. (*B*) Hypothetical schema of the relationship between lung cancer risk and screening benefit. COPD = chronic obstructive pulmonary disease; LCS = lung cancer screening.

After formal presentations, the chairs moderated breakout sessions that included all participants, with the goal of expanding the discussion and developing research questions. The breakout sessions focused on lung cancer risk (including risk prediction, special considerations for patients with COPD, and risk communication) and treatment of screen-detected lung cancer (including sublobar resection, thoracoscopy, and nonsurgical treatment), and during the discussions, the first set of research questions was drafted.

After the in-person meeting, a comprehensive summary of the transcribed meeting and field notes was compiled and organized by the chairs, and outlines were circulated to the writing committee. Subsequent conference calls were held to consolidate, refine, and prioritize the research questions and to identify methods to address them. The manuscript was drafted by the chairs, iteratively revised with input from the writing committee, and circulated to all meeting participants for review. The final document was approved by the ATS Board of Directors.

Results

The results are organized into four overarching topics: risk of lung cancer juxtaposed against competing risks of death, COPD, and lung cancer; communication of risks; and outcomes after treatment of screen-detected lung cancer. Each subsection includes the summary of the evidence and research gaps, followed by the research questions identified during the meeting. Table 1 provides the list of research questions and potential approaches to addressing them.

Juxtaposing Lung Cancer Risk and Competing Risk of Death from Other Causes

Summary of evidence and research gaps. Although using age and pack-year smoking history criteria for determining eligibility versus ineligibility for LCS is practical from the viewpoint of ease in implementation, it may be overly simplistic because individualized risk varies significantly owing to the influence of numerous variables (5, 6). Since the publication of the NLST, research has included secondary data analyses with modeling exercises focused on identifying specific at-risk populations as well as individualization of a person's overall risk of developing or dying of lung cancer (6, 7). Models that predict lung cancer risk by incorporating age, smoking intensity, and quit-year history as continuous variables and including additional risk factors such as race, family history of lung cancer, history of prior cancer, and COPD have the potential to identify individuals most at risk for developing or dying of lung cancer, thus reducing the number needed to screen (NNS) to prevent an LCD (6, 7). For example, within the NLST, it was shown that stratifying participants by individual risk using the $PLCO_{2012}$ (Prostate, Lung, Colorectal, and Ovarian Trial 2012) cancer model calculator was better than the NLST entry criteria of age and smoking history for determining who would develop lung cancer (7).

The benefits and harms of LCS may not, however, be linearly related to the risk of developing lung cancer. The complex interplay between baseline risk of developing lung cancer, treatment-related harms, and competing risk of death from other causes is crucial in determining the balance of harms and benefits of LCS (Figures 1A and 1B). For example, in the NLST, the cohort with the lowest 5-year risk (quintile 1) of LCD, accounting for 1% of prevented LCD, was associated with a NNSs of 5,276 and 1,648 false-positive results per prevented LCD (6). In contrast, the cohort with the highest LCD (quintile 5), accounting for 38% of prevented LCD, was associated with NNSs of 161 and 65 false-positive results per prevented LCD (6). Moreover, this highest-risk cohort (for LCD) would likely also have a high risk of comorbid conditions and competing causes of death, which would work to reduce the life-year gains in this very high-risk group. In subsequent analyses of the NLST, COPD prevalence increased with increased lung cancer risk according to the $PLCO_{2012}$ risk model (Figure 2) (3), and the risk of non–lung cancer deaths was greater than the risk of LCD (Figure 3) (8). Furthermore, as the risk of lung cancer and the prevalence of comorbidities increase, the ability of individuals to tolerate diagnostic procedures or treatment for a screen-detected cancer decreases (a fact not taken into account in existing models). Thus, in individuals at high risk of lung cancer, the greater risk of death not related to lung cancer, harms from procedures, and diminished ability to treat a screen-detected cancer may undermine the benefits of screening. A population-based survey found that life expectancy was lower in individuals eligible for LCS using U.S. Preventive Services Task Force criteria when compared with NSLT participants (19.6 vs. 21.2 yr), likely reflecting that individuals in the general population were older and more likely to be current smokers and to have diabetes, stroke, or heart disease (9).

Estimating the risk of developing lung cancer and success of treatment and then comparing these with the risk of dying of a competing cause is crucial. Models that accurately predict noncancer mortality risk are needed and may help to improve patient selection for LCS. Furthermore, for such models to be applicable for individual prediction, the area under the receiver operating characteristic curve is recommended to be greater than or equal to 0.80 (10). Incorporating severity of comorbidities and functional status into a noncancer mortality risk model may improve the area under the receiver operating characteristic curve but may render such a model too complex for use.

Risk prediction models do not account for potentially increased treatment-related risk in those with increased risk for the development of lung cancer. A comparison of outcomes of smokers aged 65 years or older diagnosed with stage I NSCLC in the NLST with a National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER)-Medicare cohort meeting NLST age criteria with similar low comorbidity scores (Charlson comorbidity index [CCI], 0–1) revealed no difference in perioperative surgical mortality or 5-year lung cancer–specific mortality; however, 5-year all-cause survival was lower in the SEER NLST-eligible cohort (73.6% vs. 63.8%) (11). Furthermore, in the SEER NLST-ineligible patients (e.g., CCI, $\geq$2), perioperative mortality was almost doubled, and 5-year survival was significantly lower (47.1%; $P \leq 0.0001$) (11). Individuals eligible for LCS who have a higher comorbidity burden may not benefit from screening, owing to death resulting from competing causes (Figure 4) (12). As such, it is conceivable that maximum screening benefit (e.g., decreased lung cancer mortality) may result from screening those in the middle quintiles of risk (e.g., quintiles 2–4). An approach focusing on screening outcomes such as decreased deaths resulting from lung cancer rather than solely on lung cancer risk may have utility

Table 1. Identified Research Questions by Topic: Incorporating Coexisting Chronic Illness into Decisions about Patient Selection for Lung Cancer Screening

Question	Possible Research Methods
Risk prediction	
1. At what threshold of competing causes of death should screening not be offered?	Development of models that predict noncancer mortality risk, incorporate severity of comorbidities and functional status
2. What is the preferred method to quantify the severity and burden of comorbidities among patients referred for LCS?	Survey-based risk prediction models that use self-reported variables (including sex, race, and medical comorbidities such as COPD, hypertension, CVD, and diabetes) to predict all-cause mortality may be leveraged to focus on LCS outcome Development or refinement of index scores that include contributions of multiple comorbid conditions together with severity. CISNET microsimulation modeling (incorporating comorbidity data into CISNET models) may inform factors such as quality of life and cost effectiveness of LCS in patients with and without comorbidities.
3. Should functional assessment, comorbidity severity, or both be included in models assessing competing causes of death, and how can this be effectively accomplished?	Comparison of outcomes in patients based on varying models
4. What are the ethical issues concerning withholding LCS from individuals at very high risk for competing causes of death?	Qualitative studies, surveys, consensus-building methods (e.g., Delphi) to assess patient, provider, and policy maker opinions
COPD and lung cancer risk	
5. What is the ratio of benefits to harms of LCS among patients with advanced COPD?	Comparison of outcomes in patients screened for LCS with COPD. "Watch the Spot" study includes incidental and LCS-detected lung nodules in "real-world" population of patients and will collect observational data on harms of nodule evaluation
6. Does functional status information facilitate identification of individuals with advanced COPD who may not benefit from or may be harmed by LCS?	Incorporation of functional status (e.g., BODE index) in databases of LCS patients and comparison of outcomes
Communication of risk with patients	
7. What information and which approaches optimize understanding and shared decision-making among patients with multiple comorbidities or limited life expectancy?	Qualitative and mixed-methods studies
8. How can providers best be supported in discussing these sensitive topics with patients?	Qualitative and mixed-methods studies to assess impact and utility of varying decision aid tools
9. What information and which approaches are most useful to patients and providers in discussing discontinuation of annual LCS (vs. not initiating screening) when serious comorbidities limit the benefit of screening?	Qualitative and mixed-methods studies
Treatment for screen-detected cancer	
10. Does LCS followed by alternative treatments of screen-detected cancers (e.g., SBRT, sublobar resection) reduce mortality relative to no screening among patients who cannot tolerate anatomical resection?	Database analysis of outcomes in LCS patients stratified by treatment, with adjustment for confounding factors (e.g., propensity score matching, instrumental variable analysis)

Definition of abbreviations: BODE = body mass index, airflow obstruction, dyspnea rating, and exercise capacity; CISNET = Cancer Intervention and Surveillance Modeling Network; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; LCS = lung cancer screening; SBRT = stereotactic body radiation therapy.

in identifying those who receive the greatest benefit from screening (Figure 2).

Further research is needed to identify the optimal threshold (benefits of reducing risk of LCD outweighing risks of dying of another cause) at which to determine eligibility for screening. If the probability of dying of competing causes within 5 years is higher than the probability of living for 5 years (i.e., >50% competing mortality risk), the likelihood of benefit from LCS will be quite low. However, only a very small proportion of individuals have probabilities this extreme of dying of competing causes. If the threshold is reduced, however, the number of false-positive results increases, and at some point, if this threshold is used to determine eligibility for screening, there is a risk that an individual with a small net benefit may not be offered screening.

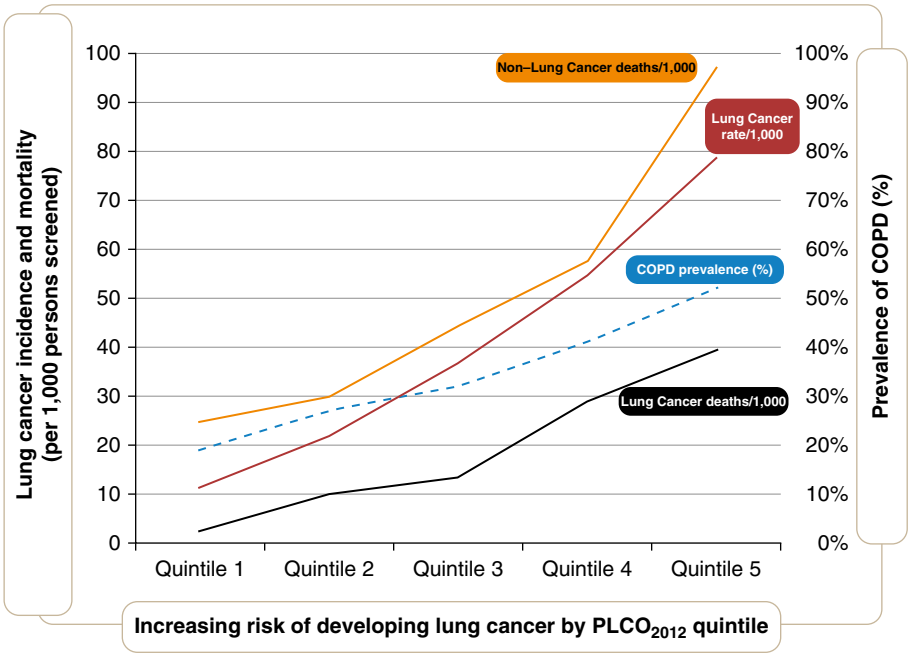

Figure 2. Relationship between lung cancer risk, lung cancer deaths, non–lung cancer deaths, and chronic obstructive pulmonary disease (COPD) prevalence according to $PLCO_{2012}$ (Prostate, Lung, Colorectal, and Ovarian Trial 2012) lung cancer risk quintile. Adapted from Reference 3.

Because any prediction model inherently has a degree of uncertainty, potential ethical issues come to light when considering using risk prediction models to identify patients who should not be offered screening owing to competing causes of death or inability to tolerate treatment for a screen-detected cancer. These models are developed and validated at the population level, and accuracy in determining individual-level outcomes is inexact.

Few studies have examined the relationship between comorbidities and lung cancer outcomes (11). A recent retrospective cohort study found that patients with lung cancer could be grouped into five distinct classes based on comorbidity profiles (defined by progressively greater CCI scores and the presence or absence of specific types of vascular disease and diabetes) that predict treatment and survival (13). Patients in class 1 were younger, had no comorbid conditions, were more likely to receive stage-appropriate therapy, and had better survival than patients in other classes despite having the least favorable stage distribution. In contrast, patients in class 5 were older, more likely to have multiple comorbid conditions (more than five), to receive no treatment, and to experience worse survival (median survival for patients in class 1 was 1.13 yr vs. 0.48 yr for those in class 5; $P < 0.0001$). The effect of comorbidity class on survival persisted when adjusted for stage and was strongest for patients with early-stage NSCLC (stages I–II), a finding that has important implications for LCS because the majority of patients undergoing LCS will be diagnosed with early-stage disease (13).

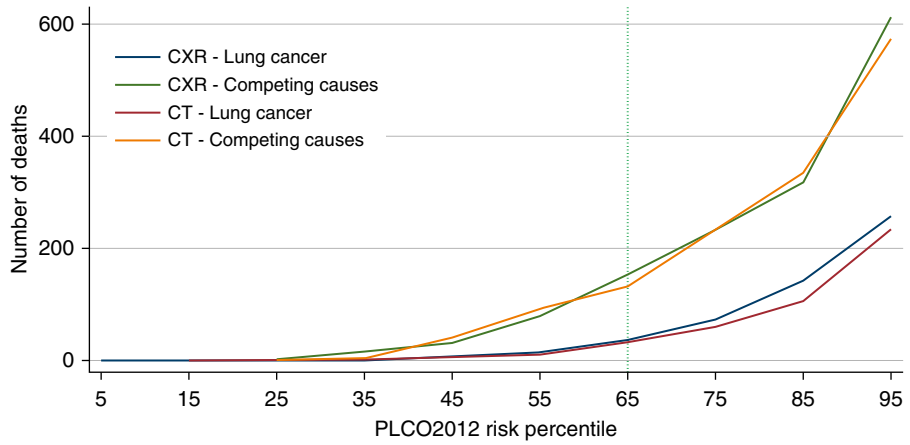

Figure 3. NLST (National Lung Screening Trial) deaths from lung cancer and competing causes by trial arm and decile of $PLCO_{2012}$ (Prostate, Lung, Colorectal, and Ovarian Trial 2012) risk. CT = computed tomography; CXR = chest radiograph. Reprinted by permission from Reference 8.

Index scores that consider contributions by multiple comorbid conditions, such as the CCI or Elixhauser comorbidity index (14, 15), are relatively simple to calculate using International Classification of Diseases diagnosis codes, have been validated to correlate with clinical outcomes, and are well studied in screening for other cancers (16–19). However, these indices have been applied mostly in retrospective research studies, have not been actively applied in LCS, and have failed to capture the severity of diseases needed to consider the effect of comorbidity in patients with lung cancer (20, 21). Furthermore, because scoring systems for the indices are based on medical practice at the time the indices are created, they may not reflect advances made in medical care and outcomes of a particular comorbid illness (e.g., survival of HIV infection 30 years ago is much different from today). In addition, there exists a strong relationship between intensity of smoking, lung function, and lung cancer risk with comorbid disease in ever smokers that is not reflected in these comorbidity indices. Suggested tools to predict noncancer competing mortality risk before patients are enrolled in LCS include clustering of comorbidities so that they are phenotypically more recognizable to the provider than a number (e.g., CCI of 4). Such a method may be easier for providers to understand and to communicate the estimated risk of dying of competing causes. Models using self-reported variables (including sex, race, and medical comorbidities such as COPD, CVD, and diabetes) have been developed to predict mortality (up to 14-yr mortality) in adults aged 65 years and older (22, 23), and these models may be leveraged to assist in determining the impact of competing risks of death on LCS outcomes.

Risk prediction: research questions.

1. At what threshold of competing causes of death should screening not be offered?

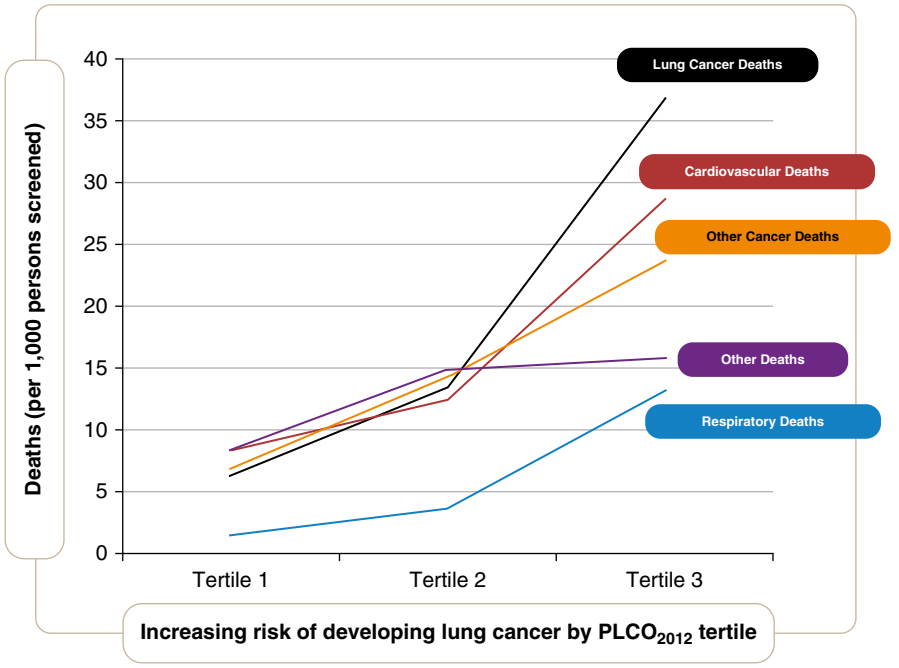

Figure 4. Deaths from competing causes according to $PLCO_{2012}$ (Prostate, Lung, Colorectal, and Ovarian Trial 2012) lung cancer risk tertile in the ACRIN-NLST (American College of Radiology Imaging Network–National Lung Screening Trial) substudy of 10,054 screening participants. Risk of lung cancer over 6-year follow-up according to the $PLCO_{2012}$ risk model with tertile 1 = lowest risk (0.27–1.94%), tertile 2 = intermediate risk (1.94–3.73%), and tertile 3 = highest risk (3.73–40.97%). Adapted by permission from Reference 12.

2. What is the preferred method to quantify the severity and burden of comorbidities in patients referred for LCS?
3. Should a functional assessment of comorbidity severity and life expectancy be included in models assessing competing causes of death?
4. What are the ethical issues concerning withholding LCS from individuals at very high risk for competing causes of death?

Modeling as a means to predict noncancer mortality risk before LCS may help determine cutoffs, but how to apply the information provided by such models needs to be established. Before setting policy or recommendations about the threshold or process to advise against LCS, research into patient, provider, and policy maker opinions on the surrounding ethical issues is needed.

COPD, Lung Cancer Risk, Competing Risk of Death, and Harms of Screening

Summary of evidence and research gaps. COPD poses a particular challenge in LCS. Although these patients have twice the risk of developing lung cancer (primarily related to emphysema) compared with smokers without COPD (6, 8, 24–27), the presence of advanced COPD may pose a significant risk for harms from LCS and downstream evaluation and treatment of screen-detected nodules. Patients with advanced COPD are significantly more likely to experience complications during evaluation of pulmonary nodules (28), develop respiratory-related surgical complications, have a higher 30-day mortality after resection of lung cancer (especially after thoracotomy) (29, 30), and have a greater likelihood of dying of causes other than lung cancer (31). Risks after transthoracic needle biopsy of a pulmonary nodule include hemorrhage (in only 1% of biopsies, but 17.8% of patients will require a blood transfusion) and pneumothorax (in 15% of biopsies, and 6.6% will require a chest tube). These complications are more common in smokers and those with COPD and are associated with longer hospital stay and respiratory failure requiring mechanical ventilation (28). In a study evaluating the safety of bronchoscopy in COPD, minor and major complications among all patients with COPD were 13% and 5%, respectively; however, respiratory complications occurred in 22% of patients with severe to very severe COPD, as compared with 6% in patients without COPD (32). Moreover, COPD, a common comorbid disease in patients with lung cancer, is associated with increased risk of death from both lung cancer and competing non–lung cancer causes (3). Given these trade-offs between potential benefits and harms of LCS, whether to screen patients with advanced COPD (severe; GOLD grades 3 and 4) remains controversial.

In screening trials (1, 33, 34) in which 20–30% of the patients had COPD (mild or moderate; GOLD grade 1 or 2), the risks from harms associated with LCS (morbidity and mortality of procedures or surgical resection) are low. For example, in the LDCT group of participants in the NLST, only 29.2% had COPD. The rates of at least one complication after a diagnostic procedure for a positive screening test in the LDCT group were only 1.4%, with no severe complications after transthoracic needle biopsy, and only 3.5% after bronchoscopy (1). However, the patients in these trials are not representative of all patients with COPD in the general population who meet age and smoking eligibility criteria for LCS. Furthermore, although pulmonary function testing with spirometry and D_{LCO} quantify and provide a physiologic assessment of COPD severity, FEV_1 only weakly predicts mortality when greater than 50% predicted and furthermore does not capture the complex nature of COPD as a systemic disease (31). Use of functional assessment may be a better means by which to quantify the degree of pulmonary impairment. The BODE (body mass index, airflow obstruction, dyspnea rating, and exercise capacity) index is one such functional assessment tool that captures physiologic impairment, patient perception of symptoms, and the two domains that express consequences of COPD (body mass index and exercise capacity) (31). With increasing BODE quartile, there is a significant increased risk of mortality, as high as 80% in 52 months in quartile 4, where patients with a higher BODE index are more likely to die of respiratory failure (61%) than of lung cancer (31). Given the complex interplay between COPD and lung cancer, further research is needed to identify the ratio of benefits to harms of LCS among patients with more advanced, severe COPD.

Factoring COPD into LCS decision-making: research questions.

1. What is the ratio of benefits to harms of LCS among patients with advanced COPD?
2. Does functional status information facilitate identification of individuals with advanced COPD who may not benefit from or may be harmed by LCS?

Individuals with COPD have a higher risk of developing lung cancer; however, the presence of advanced COPD may also pose a risk for harms from LCS and downstream evaluation and treatment of screen-detected nodules. Research to ascertain baseline risk of developing lung cancer, treatment-related harms, and competing risk of death from other causes is crucial in determining how best to risk stratify patients with advanced COPD before LCS.

Communication of Risk with Patients

Summary of evidence and research gaps. Prior research identified discussing limited life expectancy and decreased benefit of cancer screening to be challenging for providers in non-LCS contexts (35, 36). Providers vary in their comfort level regarding advising patients who meet eligibility criteria not to undergo screening owing to poor overall health or limited life expectancy (37), and a recent vignette-based survey suggested that many providers may advise patients to undergo LCS despite poor overall health and limited life expectancy (38). Although some perceive advising against LCS as excluding patients from medical care, others see it as individualizing LCS decisions by encouraging screening for those who will benefit and discouraging screening for those who will not benefit because of competing causes of death. Similarly, patients with serious health problems are divided in their opinions regarding whether and how they would like their providers to discuss limited life expectancy in the context of decision-making about cancer screening (39). Message framing is critical, but how best to do this is not clear. Examples of message framing include an interpretive statement, "LCS will not help you live longer," or the more neutral conveying of information, "Here is your risk of dying of any disease including lung cancer without LCS, and here is your risk of dying of any disease including lung cancer with LCS" (39). Message framing will vary across different groups of patients and must take into account the patient's education level, cultural beliefs, and heath literacy, including their ability to understand complex issues such as risk model concepts and competing causes of death.

Workflow considerations are critical to achieving successful implementation of the policy requirement for shared decision-making and may be especially important for more complex discussions when the anticipated benefit of LCS is marginal owing to limited life expectancy or increased risk of harms. Further research is needed to identify how best to support providers through training, education, and decision support tools. The course of the conversation, topics to be covered, and patient and provider needs and preferences for supporting these conversations may be different in the context of discontinuing annual LCS owing to development or progression of a health problem, as opposed to the context of never initiating screening because of serious comorbid disease. Given the complexity of the decision involved, it is also important to support collaborative communication among providers (e.g., primary care provider, pulmonologist, and radiologist) to avoid conflicting messages and to present a cohesive recommendation to patients.

Communicating interrelated risks: research questions.

1. What information and which approaches optimize understanding and shared decision-making among patients with multiple comorbidities or limited life expectancy?
2. How can providers best be supported in discussing these sensitive topics with patients?
3. What information and which approaches are most useful to patients and providers in discussing discontinuation of annual LCS (vs. not initiating screening) when serious comorbidities limit the net benefit of screening?

Qualitative and quantitative research investigating patient preferences regarding decisions not to undergo LCS could serve to inform these questions. Topics to explore include who is the preferred person to deliver the message (e.g., primary care provider or LCS coordinator), what is the best way to frame the message, and what are the utility and helpfulness of various decision aid tools in facilitating these conversations. There is a need for research to elicit patient and provider needs and to develop decision aids or tools that incorporate models that predict risk of dying of competing diseases and/or include sample scripts or messaging that providers could use when discussing screening or explaining why they are recommending against LCS with patients.

Treatment for Screen-detected Lung Cancer

Summary of evidence and research gaps. The U.S. Preventive Services Task Force guidelines (40) specifically suggest excluding patients unable to tolerate surgical resection, but other guidelines recommend limiting screening to those "in reasonably good health" (41) or those healthy enough to tolerate "cancer treatment" (42). These recommendations mix the simplistic exclusionary concept (no reason to screen if no treatment will be given) with the relative issues of balancing risk of LCD versus competing causes of death and morbidity, mortality, and efficacy of treatment approaches in the face of comorbidities. This confusion underlies the controversy whether eligibility for LCS should be limited to patients able to tolerate surgical resection or should include other treatment approaches, such as SBRT.

Perioperative mortality after surgical resection in LCS trials varies from 1% to 3.3% (1, 33, 34). Importantly, these trials enrolled healthy patients, and at least in the NLST, 82% of the participating centers were large academic centers and 76% were National Cancer Institute–designated cancer centers with expertise in all aspects of cancer care, including dedicated thoracic surgeons (1). Such conditions are associated with improved outcomes after surgery (43, 44) but are not universally present in community hospitals throughout the United States or other countries. In the small subset of NLST patients with stage I NSCLC who underwent radiation therapy ($n = 25$), the

5-year survival was significantly worse than that of those who had surgery (26% vs. 74%, respectively) (11). However, it is not clear exactly what this radiation therapy treatment entailed or why radiation therapy was pursued rather than surgery.

There is controversy about the relative effectiveness of SBRT versus resection. First, the data regarding SBRT involve a specific type of tumor (relatively peripheral stage I NSCLC), and thus it may not be entirely appropriate to apply these data to all screen-detected cancers. Second, observational data comparing SBRT versus resection for stage I peripheral tumors typically involve compromised patients and are inherently confounded by competing causes of death, making assessment of treatment efficacy difficult. One can attempt to minimize some of the confounding variables by assessing the inherent efficacy of SBRT versus surgery in low-risk patients.

We currently have no data on whether screening decreases lung cancer mortality among patients who are unable or unwilling to undergo anatomic resection. With regard to patients fit to undergo surgery, two small randomized trials of SBRT versus lobectomy suggested improved outcome in the SBRT group (estimated overall survival at 3 yr, 95%; 95% confidence interval [CI], 85–100) in the SBRT group compared with 79% (95% CI, 64–97) in the surgery group (hazard ratio, 0.14; 95% CI, 0.017–1.190; $P = 0.037$), but these results are difficult to interpret owing to poor accrual (combined total of only 58 patients) (45). A large National Cancer Database study of optimal patients (no comorbidities) and optimal treatment (lobectomy or full-dose SBRT) demonstrated that after propensity matching for essentially all known potential confounding factors (20 factors), the overall survival after SBRT was lower than after lobectomy (5-yr survival, 59% vs. 29%; $P < 0.001$) (46). Similar results were seen in a subset analysis of SBRT patients who had been recommended to have lobectomy but chose SBRT instead (46). Finally, a recent international survey showed that only 28% of thoracic oncology specialists (excluding radiation oncologists) believed that SBRT had a benefit the same as or better than that of resection (47). These data suggest that considering surgical resection and SBRT as equivalent treatments for screen-detected cancers is probably premature, and more evidence and examination are needed. Unfortunately, the results of several ongoing randomized trials of surgery versus SBRT among surgically eligible patients with early-stage NSCLC will not be available for several years.

Although decreasing FEV_1 and $D_{L_{CO}}$ predict worse postoperative outcomes of thoracotomy, this effect is markedly diminished for resections performed via video-assisted thoracoscopic surgery (VATS) (48–50). The perioperative mortality in advanced COPD is lower after VATS lobectomy than after thoracotomy (1.5–2.9% vs. 3.5–7.8%, respectively) (48–51). However, in U.S. population databases, only 30–40% of lobectomies are performed via VATS; furthermore, only 50% of lobectomies in the United States are performed by dedicated cardiothoracic surgeons, and only 60% of lobectomies performed by cardiothoracic surgeons are via VATS (52). Thus, the issue of how the risk of perioperative mortality should factor into a decision whether to screen a patient with pulmonary compromise is complicated: The risk is linked not only to the degree of compromise but also to the type of resection (VATS vs. open, lobe vs. segment) and where the resection may be performed. Finally, it must be remembered that competing causes of death in compromised patients may have implications that overshadow the impact of perioperative mortality when considering screening.

Treatment for screen-detected lung cancer: research questions.

1. Does LCS followed by alternative treatments of screen-detected cancers (e.g., SBRT, sublobar resection) reduce mortality relative to no screening among patients who cannot tolerate anatomical resection? Although it is unlikely that an adequately powered randomized clinical trial will be undertaken to answer this question, database analyses or modeling studies could address this issue.

Discussion

Our committee identified gaps in knowledge regarding incorporating comorbidities and competing causes of death into LCS decisions. This statement highlights the urgent need for further research that will guide clinical decision-making with patients with comorbid conditions in whom LCS harms may outweigh the benefits. Assessing the impact of comorbidities on the effectiveness of LCS is difficult. First, patients are heterogeneous, and other variables such as age, sex, and ethnicity, can interact with comorbidities and their severity. Second, isolated comorbidities vary in severity, and specific types of comorbid conditions result in different treatment and survival outcomes. Third, conditions such as COPD that increase lung cancer risk also increase the risk of death from other non–cancer-related causes. In advanced COPD, the risk for developing cancer must be balanced against increased complications during evaluation of screen-detected pulmonary nodules, higher mortality after resection of lung cancer, and greater likelihood of dying of causes other than lung cancer. Fourth, there is variability among providers regarding individualizing LCS decisions, and agreement on message framing will be critical. How best to accomplish this challenging aspect of LCS is not clear. Fifth, alternative treatments are increasingly being suggested as a way to extend LCS to a population of patients that cannot tolerate anatomical resection, but it is unclear whether LCS followed by these alternative treatments will improve mortality relative to no screening among such patients. This statement establishes a research framework for addressing essential questions about how to incorporate coexisting chronic illness into decision-making and patient selection for LCS. ■

This statement was prepared by an *ad hoc* subcommittee on coexisting chronic illness and lung cancer screening of the ATS Assembly on Thoracic Oncology.

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