

# Providing Guidance on Lung Cancer Screening To Patients and Physicians

April 23, 2012

## *Executive Summary*

Lung cancer is the leading cause of cancer death in both men and women in the United States. The disease has been closely associated with smoking since 1964, when the first Surgeon General's report concluded that tobacco smoke was a cause of lung cancer. Today, smoking is thought to cause up to 80-90 percent of lung cancer cases.

The American Lung Association (ALA) has been influential in strengthening laws and policies that protect everyone from secondhand smoke, preventing young people from starting and helping smokers quit with our smoking cessation programs. However, there remains the need to implement a comprehensive clinical strategy that assists in reducing the burden of lung cancer and increasing the significantly low survival rates. The five-year survival rate for lung cancer currently stands at 15.6 percent as compared to an over 90 percent survival rate for breast, colon and prostate cancers.

A clinical strategy for lung cancer that has showed promise is low dose computed tomography (CT) screening. The purpose of a CT screening test is to identify the presence of cancer in an individual that does not demonstrate any symptoms. In August of 2011, the National Cancer Institute released results from its National Lung Screening Trial (NLST), a randomized clinical trial that screened at-risk smokers with either low dose CT or standard chest x-ray. The study found that screening individuals with low dose CT scans could reduce lung cancer mortality by 20 percent compared to chest x-ray.

These exciting results led the ALA to reexamine their organization's current policy on lung cancer screening. As such, the ALA convened a Lung Cancer Screening Committee, chaired by Jonathan Samet, MD, MS, to review the current scientific evidence on cancer screening in order to assist the ALA in offering the best possible guidance to the public and those suffering from lung disease. This document is the first report of the American Lung Association Lung Cancer Screening Committee.

This report provides a comprehensive review of the available evidence on both the benefits and risks of lung cancer screening, as well as highlights areas where more research is needed. The Committee acknowledges that cancer screening is associated with both benefits and risks and unfortunately, the NLST could not answer a number of questions on the advantages and safety of screening in the general population. In spite of this, the Committee provides the following interim recommendations:

- The best way to prevent lung cancer caused by tobacco use is to never start or quit smoking.
- Low-dose CT screening should be recommended for those people who meet NLST criteria:
  - current or former smokers, aged 55 to 74 years
  - a smoking history of at least 30 pack-years
  - no history of lung cancer

- Individuals should not receive a chest X-ray for lung cancer screening
- Low-dose CT screening should NOT be recommended for everyone
- ALA should develop public health materials describing the lung cancer screening process in order to assist patients in talking with their doctors. This educational portfolio should include information that explains and clarifies for the public:
  - the difference between a screening process and a diagnostic test
  - the benefits, risks and costs (emotional, physical and economic)
  - that not all lung cancers will be detected through use of low dose CT scanning
- A call to action should be issued to hospitals and screening centers to:
  - establish ethical policies for advertising and promoting lung cancer CT screening services
  - develop educational materials to assist patients in having careful and thoughtful discussions between patients and their physicians regarding lung cancer screening
  - provide lung cancer screening services with access to multidisciplinary teams that can deliver the needed follow-up for evaluation of nodules.

Our hope is that this report will serve ALA well in its mission to guide the public on this very important personal and public health issue. We believe that the report, and the educational materials that stem from it, will be invaluable to the tens of million people at risk for lung cancer.

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## **1. Introduction: Why was this statement written?**

### **1.1 General Background**

Lung cancer is the leading cause of cancer death in the United States and worldwide. While the majority of cases are attributable to tobacco smoking, an avoidable cause, there are still approximately one billion smokers in the world notwithstanding of primary prevention efforts. In spite of decades of research on diagnosis and therapy, survival rates remain poor, and are reported at about 13-15% five-year survival.<sup>1</sup>

Since the epidemic of lung cancer first emerged in the 1950s, strategies for secondary prevention through screening have been evaluated, including chest x-ray initially and then sputum cytology. While these approaches have been proven not to be efficacious, more recently, there has been great interest and expectation with regard to screening by low-dose helical CT (CT), the topic of this report.

Prevention of disease with screening involves detection of disease at an early stage, such that intervention at that point improves survival. Screening is best evaluated with a randomized clinical trial, involving comparison of disease-specific mortality (or all-cause mortality if appropriate) to that in a comparison group that has received the usual standard of care, whether or not screening is part of that comparison. A randomized clinical trial measures efficacy, i.e., how well does the screening test work in the rigorous circumstances of a trial. In considering whether a screening test should be implemented, the effectiveness that will be achieved in actuality is also a critical consideration and an outcome that may vary from population to population and over time.

Over the many decades since the lung cancer epidemic began, several approaches that seemed potentially efficacious for lung cancer screening were considered and assessed, notably: mini- and conventional chest radiographs (x-rays) and sputum cytology. However, clinical trials completed several decades ago showed that screening programs using these modalities were not efficacious. More recently, prompted by observational evidence first reported about a decade ago that CT scans may be effective in screening, the National Cancer Institute carried out the National Lung Screening Trial (NLST), a randomized clinical trial that screened at-risk smokers with either CT or standard chest x-ray. The key finding, first released in November, 2010, was a 20% reduction in lung cancer mortality in the CT arm.<sup>2</sup> While promising and important, this demonstration of efficacy raises a series of complicated issues with regard to the use of CT screening in the general population, which includes millions of smokers in the United States potentially eligible for screening. Some of these general issues are:

- How effective will CT screening be in actual clinical practice, compared with the efficacy achieved in the NLST?
- In the general population (vs. the NLST), what are the risks of work-up of nodules identified with CT screening?
- How do the risks and benefits vary across different groups of smokers, including smokers with coronary heart disease, chronic obstructive pulmonary disease (COPD) and older people?
- Will availability of an efficacious screening test reduce rates of smoking cessation and possibly increase initiation, thereby increasing the number of current smokers?
- What are the potential costs of using CT screening for lung cancer? How will costs of screening be covered?

As “...the leading organization working to save lives by improving lung health and preventing lung disease...”, the American Lung Association (ALA) has great interest in these issues, particularly as it communicates to the public which turns to it for long-trusted guidance on lung health. People with COPD are a key constituency for the ALA and for this group particularly, the risks of work-up and therapy may be substantially greater than for participants in the NLST.

The present committee was assembled by the ALA and charged with providing guidance to the ALA as it develops its public stance and policy messages with regard to the NLST. Here, we offer initial recommendations to the ALA to assist the organization in offering the best possible guidance in the short-term to its diverse constituencies. For the longer-term, we also offer a strategy for further development of the scientific and policy foundation for implementing screening based on the NLST findings. We give particular emphasis to risks and benefits among groups at high risk from diagnostic procedures and therapy.

## **1.2 Stakeholder Concerns and the ALA**

As important background for the development of this report, the committee was informed about the challenges faced by the ALA in responding to stakeholder questions about lung cancer screening, both before and after the NLST findings were released. These challenges were central in our planning, as we recognized that recommendations from this initial report and any follow-up activities needed to provide an evidence-based foundation to ALA for its responses and positions.

The ALA faces the challenge of advising the public and particular stakeholder groups on diverse issues related to CT screening. In advising the public, it bases its advice to the extent possible on interpretation of the relevant evidence, carefully evaluating its strengths and weaknesses. The ALA also looks carefully at the broader context in offering guidance. The topic of screening and the potential to avoid cancer are of great interest to the public, particularly those at increased risk for a disease, as with lung cancer among smokers. Even the possibility that screening might detect cancer motivates many to seek screening. Obtaining a screening test may be viewed as having “no regrets” since there seems to be the possibility of a negative test or of finding a cancer at an early stage. Thus, people may see no harm in obtaining a screening test and stakeholder groups may advocate for use of a test, even when usual criteria for strength of evidence for recommending a test are not met.

Various groups will be reviewing and evaluating the NLST evidence for the purpose of developing guidelines for lung cancer screening. The US Preventive Services Task Force (USPSTF) has this role within the Department of Health and Human Services. Based on the

results of the NLST, this group will eventually update its current recommendation, which does not currently support screening for lung cancer.

A few other groups have already released guidelines or reports regarding lung cancer screening based on the NLST results. The American Cancer Society interim guidance on screening suggests that people who meet the NLST entry criteria may consider screening, but it offers cautions and recommends that people having CT screening should do so in institutions with appropriate multidisciplinary teams available.<sup>3</sup> The International Association for the Study of Lung Cancer (IASLC) Board of Directors convened a computed tomography (CT) Screening Task Force to develop an IASLC position statement. A recently published report of the workshop proceedings sets out a strategy for approaching CT screening.<sup>4</sup>

A number of other organizations are in the process of interpreting the NLST results to develop their own guidelines or recommendations. Unfortunately, even before the NLST results were released, CT screening for lung cancer was being offered by some institutions and subsequent to the release an increasing number of well-respected medical centers throughout the country are offering lung cancer screening to their constituents at markedly reduced prices.

The ALA has also been fielding questions from the public since the release of NLST. Some of the more common questions are as follows:

- Why does the American Lung Association not support CT screening for lung cancer given the NLST trial results and the success of screening for other cancer types?
- If the ALA does not support CT screening, what can I do to detect lung cancer early?
- If I am considered at high risk for lung cancer, should I be screened? What does it entail?
- What should I look for as essential and recommended features of the facilities that would conduct this procedure and manage its possible aftermath?

### **1.3 Committee Approach**

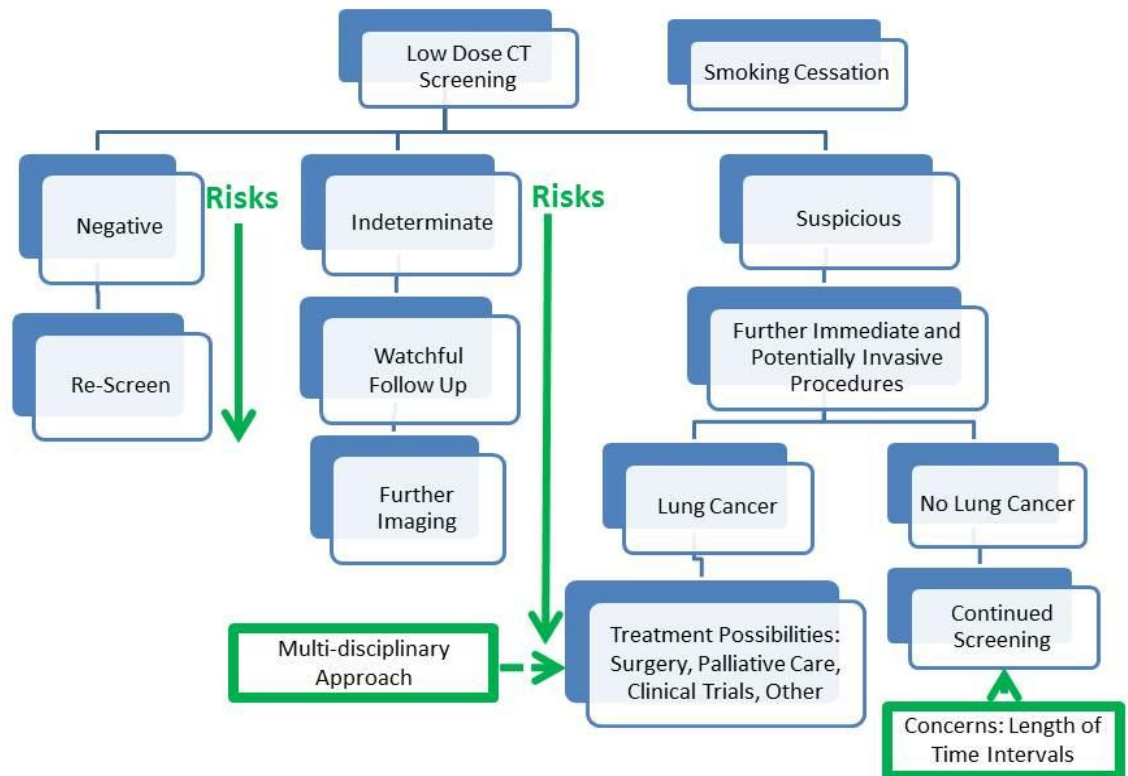
We note that there are numerous groups that develop recommendations for disease screening. In the United States, the US Preventive Services Task Force (USPSTF) is the government entity that develops guidelines for cancer screening based on a well-established evidence-based review strategy.<sup>5</sup> To date, this group has not recommended screening for lung cancer. In adhering to a strict, evidence-based approach, some of its recommendations have surprised the public and proved remarkably controversial: e.g. mammographic screening for breast cancer in women under age 50 years and use of PSA testing. Our goal is not to replicate the future efforts of the USPSTF, but to examine the available evidence in order to advise the ALA on guidance that it should be offering at present, before such organizations have reviewed the evidence and made recommendations and to make recommendations for expansion of that evidence that will be of value to the ALA as it provides evidence-based guidance to the public.

In developing this report, the committee, a multidisciplinary group that included the broad spectrum of expertise needed to consider lung cancer screening, reviewed the NLST and scanned for other trials in progress. It also considered initial responses from various expert groups and other commentary in the aftermath of the report from the NLST. It noted the marketing of CT screening that intensified following release of the NLST findings. Largely, however, the committee used its collective judgment to provide interim guidance to the ALA and to set a course to obtain evidence that would target key uncertainties, with particular reference to the ALA's stakeholders.

For the purpose of this report, the committee identified two broad groups of stakeholders from the ALA’s perspective. One constitutes the diverse groups of people who are at risk for lung cancer and who turn to the ALA, as a trusted voice, for guidance. This broad group has multiple components: people who have smoked and are concerned with the possibility of developing lung cancer, the families of such people, people with COPD and asthma, and health care professionals involved in the care of people at risk for lung cancer. The second includes institutional groups who also value the views of the ALA: other organizations involved with public health and clinical issues, policy-makers within the government, and health care organizations, for example. This report focuses on those issues related to the first stakeholder group, a higher priority for the ALA at present. In a planned second report, the committee will turn to issues related to the second stakeholder group.

In considering the implications of the NLST findings, the committee developed a general framework for describing the process of screening for lung cancer, moving from a decision to undergo a CT screening through the various steps and decision points that follow. Figure 1 portrays the screening process from the perspective of the individual who may decide to be screened. A decision to have a CT screening may be followed by multiple scenarios, some involving risk for morbidity and even death, and the possibility of further screening in the future. The NLST only addresses one aspect of this framework—does screening lead to a reduction of lung cancer mortality? The committee includes smoking cessation in the figure as a reminder that it should be recommended throughout the screening process.

**Figure 1: What Happens If I Choose to Be Screened?**

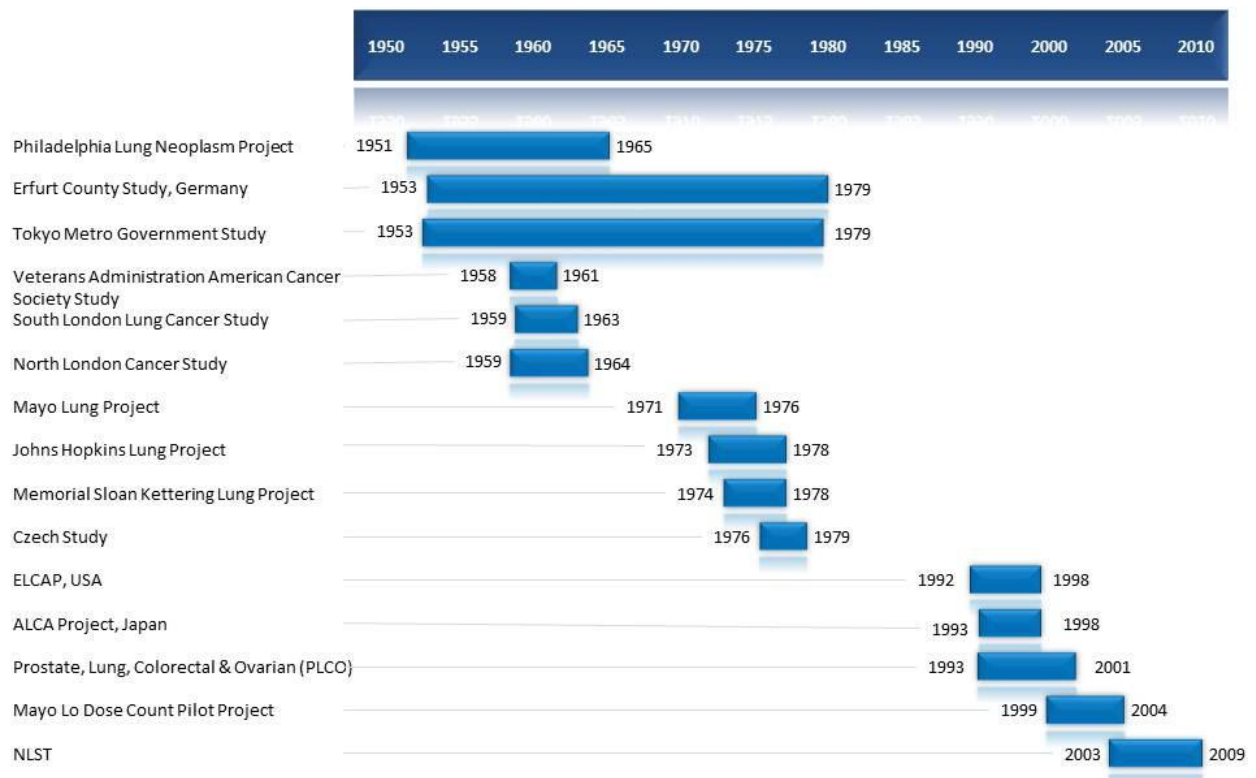


## 2. What have we learned from the NLST?

### 2.1 State of evidence prior to NLST results

Given the poor natural history of lung cancer, there has long been interest in the possibility of reducing the burden of premature mortality by screening. Prior to the NLST, lung cancer screening approaches have focused on the use of chest x-ray and sputum cytology. Figure 2 provides a timeline of previous lung cancer screening trials.

Figure 2: Study Timeline



Chest x-ray had been successfully used for decades to identify tuberculosis in earlier, more treatable stages, and by the early 1950s it was used in widespread TB screening efforts. Four different studies using chest x-rays for lung cancer screening were launched in the 1950s in Philadelphia<sup>6</sup>, South London<sup>7</sup>, Tokyo<sup>8</sup> and within the United States Veterans Administration<sup>9</sup> to determine if lung cancer survival could be improved by regular, frequent chest x-ray. The number of subjects enrolled in these studies ranged from just over 6,000 to more than 1.8 million, with 3 of 4 studies involving chest x-ray every 6 months<sup>6,7,9</sup> and the fourth study obtaining an annual chest x-ray<sup>8</sup>. However, control groups were not included in these studies, and the end points focused on comparing survival rates in the group with frequent chest x-rays to historical rates. Although patients who underwent surgical resections had improved 5-year survival rates, overall survival in all studies was not different in screened groups compared with historical comparison groups.

Two other studies performed at about this time did recruit control groups. The North London Lung Cancer study began in 1960, enrolling almost 55,000 subjects to evaluate whether chest x-

rays at 6-month intervals improved lung cancer mortality compared to a control group in which chest x-rays were obtained only on entry and at the end of the study.<sup>10,11</sup> Current, former and never smokers were recruited from industrial areas, and participants were required to be 40 years of age or older. The Erfurt County, Germany study began in 1953 and enrolled over 143,000 subjects, of which 41,000 underwent chest x-rays every 6 months and 102,000 had chest x-rays at 18-month intervals.<sup>12</sup> Only men were enrolled in these studies, as the vast majority of smokers at that time were male. In both studies, the more rigorous screening schedule detected more cancers that were surgically resectable than were found in the less rigorous chest x-ray schedule; 5-year survival was higher in the more frequently screened group. At about the same time there was also considerable interest in sputum cytology as a lung cancer screening tool. Saccomano and associates reported a method adapted from the Papanicolaou technique for preparing sputum samples for cancer cell evaluation.<sup>13</sup> Case series and small studies also reported diagnosis and successful treatment of radiographically-negative lung cancers detected by sputum cytology.<sup>14,15</sup> A large cooperative study of the Veterans Administration and American Cancer Society confirmed that obtaining sputum samples for cytologic evaluation from participants in a large clinical trial population was feasible, with sensitivity and specificity similar to chest x-ray.<sup>9</sup> Based on these findings, the National Cancer Institute (NCI) Cooperative Early Lung Cancer Detection Program was initiated at 3 different institutions in the early 1970's: Johns Hopkins University, Memorial Sloan Kettering Cancer Center, and the Mayo Clinic.

The Hopkins and Memorial studies had similar designs.<sup>16,17</sup> Each site had a target enrollment of 10,000 men aged 45 or older with a smoking history of 1 pack per day for at least 1 year. All subjects received an annual chest x-ray; however, subjects were randomized either into an arm that also provided sputum for cytologic analysis every 4 months ("dual screening"), or to an arm in which sputum was not obtained. Although prevalence screening detected a predominance of Stage I cancers which initially showed improved survival, there were no differences in number of lung cancer cases detected and no difference in mortality rate between the two study arms in these trials.<sup>18,19</sup> Long-term follow-up confirmed that cancers detected by either screening arm had a higher proportion of Stage I cases, with accompanying improvements in survival, compared to cancers detected during intervals between screening or during the post-screening follow-up period.<sup>20</sup> Improvements in survival were also noted to be superior for the United States during that time although, as in earlier reports, no differences in mortality were found.

The design of the Mayo Lung Project was slightly different.<sup>21,22</sup> The control group was assigned to receive "standard care" as practiced at the Mayo clinic at that time, which was to receive yearly chest x-ray and sputum cytology. The intervention group underwent dual screening, i.e., subjects received chest x-ray and provided sputum samples for cytology, every 4 months. As in the Hopkins and Memorial studies, no differences in mortality were noted between subjects undergoing more rigorous screening and subjects in the standard care group. However, the rigorous screening group had more lung cancers detected with a higher percentage of localized cancer that was eligible for curative surgical resection. Five-year survival was increased for lung cancers detected by screening, but there was no difference in mortality rates between the two trial arms.<sup>21,23</sup> Long-term follow-up showed that subjects in whom cancer was detected by the rigorous screening approach had better survival, but mortality improvement was not confirmed.<sup>24</sup>

A similar study was performed in Czechoslovakia.<sup>25</sup> Over 6,300 men were either randomized to undergo chest x-ray plus sputum cytology every 6 months for 3 years, or to a control group that underwent chest x-ray plus sputum on entry in the study and at the end of 3 years. Eligibility



criteria for the study included men 40-64 years of age who were current smokers with at least 150,000 cigarettes smoked in lifetime (approximately 20 pack years). Subjects were allocated into either group by a computer program to keep demographics, place of residence, smoking habits, occupational exposures (to potential carcinogens) comparable in the two groups. Similar to the Mayo Lung Project, more cancers were detected in the semi-annual screened group with a larger number of early stage cancers. However, there were a similar number of late stage cancers. There was no difference in lung cancer or all-cause mortality during the initial 3 year period or after prolonged follow-up.<sup>25,26</sup>

These earlier studies were begun at a time when the need for carrying out randomized controlled trials of screening had not yet been identified. Based on the experience with tuberculosis, the use of chest x-ray seemed appropriate and justified and demonstration-like projects were initiated. Thus, all of these earlier screening studies had significant limitations with regard to evaluation of chest x-ray as a screening tool. In particular, these studies had poor compliance with the designated chest x-ray protocol and high attrition rates.

With the exception of the NCI Cooperative and the Czech studies<sup>16,17,22,25</sup>, these early studies did not include control groups, and focused only on comparing results of the study cohort with historical outcomes. Thus, while improvements in 5-year survival were noted in screened populations in some of the studies, the effect in the population being studied could not be evaluated. However, two of the three NCI Cooperative studies essentially only tested sputum cytology as a screening tool in a controlled fashion; the “control” group in each study had yearly chest x-ray, thus only comparing annual chest x-ray to a more rigorous regimen of chest x-ray every 4 months. The Czech study included both sputum and chest x-ray at beginning and end of the study in the control group, and the Mayo Lung Project “suggested” that subjects in the control group have yearly chest x-ray and sputum. Thus, the Czech and Mayo projects also essentially compared more versus less rigorous screening with both chest x-ray and sputum cytology. Differences in survival were noted in some of the more rigorous screened groups in these studies, although no differences in mortality were found, suggesting that lead- or length-time and over-diagnosis biases may have played a role in the results of these studies.

Since none of these studies included an arm without any chest x-ray screening, the value of chest x-ray by itself for lung cancer screening was still debated.<sup>27</sup> This issue was addressed by the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial, which began in 1993 and enrolled approximately 150,000 participants.<sup>28</sup> In this study, patients were randomized to either receiving annual chest x-ray or “usual care” by their providers for 3 years and then followed until study completion (median follow-up of almost 12 years). Importantly, the usual care group “contamination” rate was estimated at only 11%, as defined by the proportion of usual care subjects having a chest x-ray as part of a routine physical examination. Results showed an equal number of cancers detected in the screened and usual care groups, with no differences in lung cancer stage distribution and no differences in cumulative lung cancer incidence between the groups. As smoking was not a prerequisite for PLCO eligibility, a subset of patients who met criteria for enrollment into NLST were also evaluated (i.e., current or former smokers with greater than 30 pack years and no more than 15 years of smoking cessation). Similar to the overall study findings, no difference in cumulative lung cancer incidence was noted between the screened and usual care patients in this subgroup.

Thus, lung cancer screening trials to date have not demonstrated improvement in lung cancer mortality using either chest x-ray or sputum cytology. While early trials did show that these tools

were able to detect lung cancers at early stages, no decrease in late stage cancers was noted in intervention arms, a finding suggesting that over-diagnosis bias may have contributed to these results. Most importantly, lung cancer mortality was consistently unimproved by these methods in all trials. The recent results of the PLCO, which included a true non-screening arm in its design, confirmed the lack of efficacy of chest x-ray for lung cancer screening.

The advent of CT technology provided the possibility of a more thorough evaluation of the entire lung parenchyma at higher resolution than possible with chest x-ray, making CT screening an enticing tool for detecting small, early stage cancers. CT is a scanning technique that uses low doses of radiation which significantly reduces radiation exposure but preserves much of the resolution required to detect small nodular opacities in the lung. Initial results from a program conducted by the Anti-Lung Cancer Association (ALCA), a for-profit organization in Japan which offers yearly lung cancer screening exams for members, showed that annual CT screening could detect small, asymptomatic lung cancers that were mainly Stage I and surgically resectable.<sup>29</sup> A follow-up report on the ALCA screening initiative confirmed these results, showing that 78% of cancers in prevalence CT screening were Stage I, as were 82% of cancers found during incidence screening.<sup>30</sup> Cancers detected with CT had an 85% survival rate, much better than historical rates demonstrated in cancer registries. Similar findings were reported by another Japanese group using mobile CT scanners.<sup>31</sup>

In 1999, the initial findings of Early Lung Cancer Action Project (ELCAP) were reported.<sup>32</sup> Subjects in the ELCAP were 60 years of age or older and had a 10 pack year history of smoking. In an initial prevalence screen of 1,000 patients using CT, 233 (23%) of subjects had non-calcified nodules. Twenty seven were diagnosed with lung cancer, of which 85% of the detected cancers were Stage I, mostly adenocarcinomas; all but one was surgically resectable. In a follow-up report, 841 of the original subjects underwent repeat CT screening annually.<sup>33</sup> Nodules were identified in another 63 subjects, 23 of which could actually be located on an earlier screening study when reviewed; all of the nodules in these patients were 5 mm or less in diameter. Eight of these subjects were referred for biopsy of nodules suspicious for lung cancer, and 7 were found to have cancer, 5 Stage I.

The Mayo Clinic began a prospective CT screening study of patients at high lung cancer risk in 1999.<sup>34</sup> Subjects underwent baseline CT screening, then annual screening for 4 more years. Eligibility criteria were more stringent than ELCAP and the trial focused on screening subjects with heavy cigarette smoke exposure history. Over 50% (n=780) of subjects had nodules on initial screen and 22% (n=338) had nodules identified on subsequent screening. Notably, nodules were found in 74% of subjects over the 5-year time period of the study. The false-positive rate for nodules (those that were not eventually diagnosed as lung cancer) was 92% for all nodules and 96% for nodules > 4 mm; 69% of patients had a false-positive result at some point during the 5 years of the study. Lung cancer was diagnosed in 66 (4%) subjects, 31 during the prevalence screen, 32 during incidence screening and 3 between screening intervals. Prevalent cancers were mostly adenocarcinomas (including bronchioloalveolar carcinomas), but the incident cancers had a higher proportion of squamous cell histology (29%) compared to prevalent cancers. Sixty-one percent of cancers detected by CT scans were stage 1, somewhat less than in other studies examining CT screening.

Currently, there are a number of ongoing studies evaluating CT screening for lung cancer in Europe and some will evaluate issues not addressed by the NLST. For example, the NELSON trial is a population-based randomized clinical trial comparing CT screening to “usual care” (not chest x-ray).<sup>35</sup> These investigators are also interested in developing strategies to minimize the false-

positive rate caused by non-cancer-related nodules using radiologic methods.<sup>36</sup> These and other ongoing studies will complement the NLST results, and hopefully lead to expanding the foundation for decisions regarding recommendations on CT screening for lung cancer.

## 2.2 NLST results

Results from the National Cancer Institute's National Lung Screening Trial (NLST), published in the *New England Journal of Medicine* in August 2011, revealed that screening high-risk individuals with CT scans reduced lung cancer deaths by 20.3 percent compared to chest x-ray (247 deaths per 100,000 person-years vs. 309 deaths per 100,000 person-years).<sup>2</sup> This result was statistically significant. The NLST researchers found that one death could be prevented for every 320 people screened with CT.

The trial, which was ended early due to these promising results, enrolled participants who were current and former smokers with no history of cancer, who smoked the equivalent of one pack a day for 30 years, and were between the ages of 55–74 years old. Roughly 7 million out of 94 million current and former smokers in the United States fit this demographic.

Key NLST participant characteristics:

- 70% were between the ages of 55-64 years on enrollment.
- 59% were male
- 91% were White and 5% were Black
- Less than 2% were of Hispanic origin
- 50% were current smokers; 50% were former smokers

Participants were randomly assigned to receive three annual screening exams with either a CT scan or a chest x-ray, and were then followed for another 5 years. The rate of adherence to screening was more than 90%. In all three rounds, the rate of positive screening tests, defined as the discovery of a nodule at least 4mm in any diameter or other abnormalities that were suspicious for lung cancer, was substantially higher in the CT group than in the chest x-ray group. Thirty-nine percent of participants in the CT group had at least one positive screening result compared to 16% in the chest x-ray group. Over the three rounds, 24 percent of participants screened with CT had a positive finding compared to only 6.9 percent of those screened with chest x-ray. Identification of clinically significant abnormalities other than lung cancer was three times as high in the CT group as in the chest x-ray group.

More than 75 percent of the positive screening tests over the three rounds resulted in a diagnostic evaluation. The diagnostic evaluation most often consisted of further imaging; invasive procedures such as biopsy and surgical procedures were infrequently performed. A total of 96.4 percent of the positive screening results in the CT group and 94.5 percent in the chest x-ray group were considered false-positive results – probably due to the presence of benign intrapulmonary lymph nodes or non-calcified granulomas. Adverse effects from the screening test and subsequent diagnostic procedures were few and minor. Deaths as a result of the diagnostic evaluation were also rare.

The incidence of lung cancer was 13 percent greater in the CT group compared to the chest x-ray group (645 cases per 100,000 person-years vs. 572 cases per 100,000 person-years). The majority of lung cancers detected by the CT scan and chest x-ray were in earlier, more treatable stages; however, this distribution was more favorable in the CT group. Non-small cell lung cancers, such as adenocarcinomas and squamous cell lung cancers, were the predominate type found by both

CT scans and chest x-rays. Unfortunately, the more aggressive type of lung cancer, small cell, was not detected in early stages by either group.

The generalizability of these results to the general population remains unanswered. The NLST implemented very strict inclusion criteria which did not include other subgroups at high risk for lung cancer. In addition, trial participants were younger and had a higher level of education than a random sample of smokers 55 to 74 years of age, characteristics which might have increased adherence to the study protocol. The study also did not provide insight as to what would be the optimal method of CT screening in the general population. Lastly, the NLST was conducted at medical institutions recognized for their expertise in radiology and in the diagnosis and treatment of lung cancer. It is possible that community facilities will be less prepared to undertake screening programs and the medical care that must be associated with them.

### **3. What are the key uncertainties from the perspective of the American Lung Association?**

#### **3.1 Lack of information on pulmonary disease characteristics of NLST participants**

One key issue in generalizing the findings of the NLST relates to the characteristics of its participants, including the distribution of lung function level and the percentages with COPD, other lung diseases and coronary heart disease. These characteristics are key determinants of tolerance of diagnostic procedures and the potential for having surgical resection with an acceptable rate of complications. Additionally, there is a known bias such that persons agreeing to participate in clinical trials are healthier than those who do not participate and also meet eligibility criteria. There is an additional tendency for those remaining in a trial to be healthier than those who are lost to follow-up and censored.

#### **3.2 Screening yield by level of lung function**

Chronic tobacco smoke exposure is a leading cause of lung cancer. Increasing evidence shows that those at greatest risk for the development of cancer are smokers who develop COPD and have emphysema on their CT scan, although the underlying mechanism for this association is unclear.<sup>37</sup> Results of the recently completed NLST investigation suggest that CT screening of smokers may reduce the risk of death due to lung cancer.<sup>2</sup> It is, however, impractical to propose such screening in all smokers and further investigation is needed to determine those at greatest risk and who may experience the greatest benefit from such intervention.

Multiple studies have shown that reduced lung function is a general mortality risk factor and an important risk factor for lung cancer.<sup>38,39</sup> There is the possibility that confounding contributes to this association and the lower level of lung function may be indicative of having received a larger dose of tobacco smoke components to the lung, compared to smokers who maintain normal lung function. However, there is a general consensus that reduced forced expiratory volume in 1 sec (FEV<sub>1</sub>), a measure of lung function, at baseline is significantly associated with an increased risk of lung cancer.<sup>38,40–47</sup> Although baseline health status, degree of abnormality in lung function and length of follow up varied considerably among the cohorts studied, the findings of an association between lung function on enrollment and lung cancer risk were remarkably similar.

Independent of cigarette smoking history, reduced FEV<sub>1</sub> is associated with an increase in the risk for lung cancer in the general population. Several aspects of this relationship are relevant in identifying high-risk groups for lung cancer screening:

- The relationship is severity dependent such that individuals with the worst lung function have the highest risk whereas those with preserved lung function have the lowest risk.
- The relationship is non-linear; relatively small differences in FEV<sub>1</sub> which are commonly considered within the normal range (for example, from 100% of predicted to 90% of predicted) is associated with an increase in the risk of lung cancer by 30–60%. New findings suggest that among people with COPD, lung cancer occurs more frequently in older patients with milder airway flow obstruction<sup>48</sup> and lower body mass index.<sup>49</sup>
- The risk is gender dependent and appears to be amplified in women.<sup>39</sup>

Reduced lung function also has physiological and histopathological effects that may affect CT screening for lung cancer in multiple ways:

- Reduced quality due to impaired ability to perform a breath-hold during CT screening. CT screening has to be performed with minimal breathing motion. Breathing motion complicates the acquisition of the CT images by inducing artifacts that may complicate its clinical validity for screening and diagnostic purposes.
- Poor lung function is associated with a higher level of emphysema. Emphysema modifies how the body absorbs the radiation to produce an image. In general, higher levels of emphysema may be associated with higher contrast levels and a reduction of CT scattering artifacts that may lead to a better solid nodule characterization on CT scans. Additionally, the presence of emphysema detected on CT scans has been shown to be an independent risk factor, as well as, a predictor of mortality for lung cancer.<sup>49–52</sup>
- Airway thickening is also related to decreased lung function from airway flow obstruction and it may also be associated with increased risk for lung cancer. Although one recent study has shown that airway thickening is not a risk factor for lung cancer<sup>50</sup>, more studies are necessary to reach meaningful conclusions about the risk of lung cancer in smokers with airway-predominant disease.

### 3.3 Complication rates by level of lung function in NLST participants

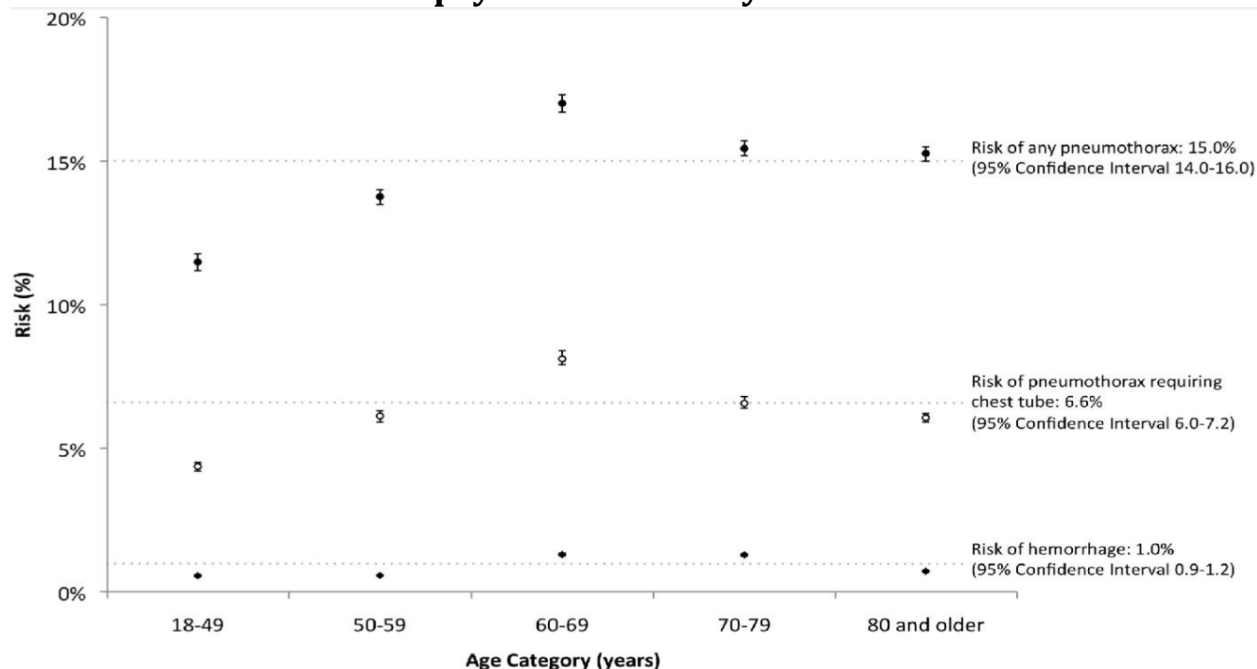
One critical issue for the ALA, given its role as a trusted advisor to people with COPD, is to be able to provide information on the risks of work-up, given the finding of a nodule. People with COPD need to understand that they face heightened risk for complications and even death if they undergo thoracic surgery. Surprisingly, few reports exist on complication rates of diagnostic procedures in relation to level of FEV<sub>1</sub>. Several older reports documented a relationship between level of FEV<sub>1</sub> and risk for pneumothorax.<sup>53</sup> One study that did not find such a relationship had limited statistical power.<sup>54</sup>

A recent report, based on administrative data bases for four states, provided population-based information on rates of complications after transthoracic needle biopsy of a pulmonary nodule.<sup>55</sup> The overall risk for hemorrhage, pneumothorax and pneumothorax requiring a chest tube was 1%, 15% and 6.6%, respectively. Figure 3 shows the risks for complications by age, with adjustment for predictors including COPD. The presence of COPD significantly increased the risk for all complications: odds ratio (OR) = 1.61; 95% confidence interval (CI): 1.08-2.39 for hemorrhage; OR=1.88 (95% CI 1.69-2.09) for any pneumothorax; and OR=2.52 (95% CI 2.16-2.95) for pneumothorax requiring chest tube.

Unlike minimally invasive biopsy techniques such as trans-thoracic needle aspiration or transbronchial biopsies, surgical biopsies are seldom used solely for diagnostic purposes as a cancer confirmed at the time of a surgical biopsy is ideally followed by completion lobectomy and

adequate lymph node dissection for staging.<sup>56-59</sup> Rates for surgical complications increase for those with lower levels of ventilatory function including pre-existing cardio-pulmonary limitations such as COPD and pulmonary fibrosis. Based on studies going back to the 1970's and 80's, complications after lobectomy increase with FEV<sub>1</sub> <1.5L, with significant increases in perioperative risk occurring if the predicted postoperative FEV<sub>1</sub> or diffusing capacity is <40%.<sup>60</sup>

**Figure 3: Adjusted Risk for Complications after Transthoracic Needle Biopsy of a Pulmonary Nodule**



Surgical approaches which result in limited resection of lung parenchyma, such as segmentectomy or wedge resection, may be better tolerated in patients with lower levels of lung function<sup>61</sup>, although it is also known that “non-anatomic” resections are associated with statistically higher risks of recurrence and reduction in survival that approaches significance in one study.<sup>62</sup> Video-assisted thoracoscopic surgery (VATS), which is less invasive than thoracotomy, has been associated with lower morbidity rates.<sup>63,64</sup> However, surgeons trained in these specialized surgical techniques may not always be available in the general community.

**3.4a Imaging quality: technical aspects and replication in community based studies**

The NLST was based on screening patients with CT scanners from GE, Siemens, Toshiba and Philips.<sup>2</sup> The scanners had to have a minimum of four channels (or detectors). All the machines used in the study met the technical standards of the American College of Radiology. The imaging protocol was designed to be as low-dose as possible (average effective dose of 1.5 mSv) to minimize radiation risk. Other image quality parameters were optimized so the variability across multiple scanners was minimal. A main factor in the protocol design was that the scanning protocol had a slice thickness of 2.0 mm and 1.8 mm.

The main technology assumption made by the NLST is that the CT scanners used in the trial had to be multi-detector scanners. The key rationale behind this decision was to be able to scan the whole chest in a single breath hold and within a time duration that was comfortable and

achievable by the enrolled subjects. Furthermore, by having more detectors, thinner slices could be obtained while keeping the acquisition time low. Multi-detector CT scanners with at least 4 detectors constitute the current practice of current community clinical facilities. Therefore, the technical implementation of the NLST protocol is within technical reach.

CT acquisition depends on several factors that play a role into the quality of the image as well as the dose delivered to the subject. Relevant factors for the task of screening are:

- Slice thickness: CT creates a 2D image of body sections by detecting the absorption of X-rays while traveling through the body. By continuously moving the gantry table across the subject chest, a stacked of images can be collected. The separation between a consecutive set of images constitutes the slice thickness, which is directly related to the scanner resolution and it has a direct implication in the quantification of nodules sizes.
- Reconstruction kernel: CT image formation is the result of an algorithmic process that transformed the detected signal to an image. A main component of this process is the use of a reconstruction kernel. The kernel is a trade-off between the in-plane image resolution that allows the detection of small details and the amount of noise in the image. Reconstruction kernels used in NLST belong to the “soft” family. The decision was driven by the need of minimize the noise effect due to low dose protocols. Extra additional information could be obtained by using “sharp” kernels while keeping image noise levels under control for the same radiation exposure.
- Radiation dose: CT image quality in terms of level of noise is directly related to the radiation dose. Image noise is related to the “grainy” aspect of CT images and directly affects the ability to visually diagnose and quantify small nodules. However there have not been rigorous studies to define the direct relation between dose and nodule detection. Radiation dose determines risk for cancer associated with imaging procedures and should be minimized.

There are also external factors to the CT acquisition process that affect image quality. Body weight is the most critical one. BMI is associated with poor image resolution due to higher X-ray absorption and artifacts like beam hardening and scattering.<sup>65</sup>

All of these factors play into the quantification of nodule size from CT images. Slice thickness can be reduced beyond the NLST protocol in future community-wide implementation of screening. Current multi-detector scans (16 detectors and higher) allow for smaller slice thickness (less than 1 mm) within a reasonable time, compared to the machines used in the NLST. As a result, nodules could be detected that are smaller than those captured by the NLST protocol. However, the trade-off is that the radiation dose is increased. Additionally, it is unknown as to whether detection of smaller nodules will improve mortality and the impact on the false-positive rate is uncertain, but it is likely to be increased.

Another aspect of screening that is now improved beyond the NLST imaging protocol is the reconstruction of the CT images. The vast majority of the scanners currently available use the same reconstruction algorithmic method based on filtered back projection (FBP). The next generation of scanners that are currently being deployed by vendors in academic centers implement what is called statistically iterative reconstruction. Iterative reconstruction makes assumptions about the scanner geometry and noise statistics to improve image quality (less noise and higher resolution) at even lower radiation levels than currently employed.<sup>66,67</sup>

Iterative reconstruction may enhance results obtained with the NLST scanning protocol in any future implementation.

A final observation should be made regarding the proper post-processing approach to quantify nodule size and rate of growth. The Response Evaluation Criteria in Solid Tumors (RECIST) working group in 1998-2000 proposed the use of the (uni-dimensional) maximal diameter as a more efficient standard estimator of lesion volume.<sup>68</sup> The RECIST guidelines are currently being challenged by the capability of using full volumetric assessment of the nodule size to better capture the growth rate in complex-shape pulmonary nodules.<sup>69</sup>

In summary, the NLST scanning protocol is technologically feasible in general community settings. Qualification standards have to be in place to certify equipment, as well as, technical personnel to perform CT for lung cancer screening. Additionally, current technological advances in CT technology and reconstruction algorithms may lead to lower dose exposure, thereby reducing concern about cancer risk and also improving image quality.

### **3.4b Evaluation of positive findings**

A critical issue to address is what constitutes a “positive finding” on a CT performed expressly for the purpose of lung cancer screening in an asymptomatic “high-risk” population; a separate and also critical decision is who is considered sufficiently high-risk to warrant screening with appropriate cost-benefit considerations and meaningful reduction of lung cancer mortality.

In the NLST, the finding of a non-calcified nodule (NCN) of greater than 4 mm diameter was considered a “positive” finding that warranted follow-up evaluation and monitoring at a level more intense than the recommended interval (annual for two years after initial baseline screening) and or diagnostic interventions (non-CT imaging studies, including contrast-enhanced dynamic CT and PET-CT, and invasive tissue diagnostic procedures).<sup>2</sup> This definition of a “positive” finding is interpreted as also being suspicious for possible lung cancer, and makes no distinction between any NCN that is greater than 4 mm versus a much more suspicious lesion based on size or other radiographic characteristics. The majority of NCNs followed in longitudinal screening studies, such as the NLST, have turned out to be benign in nature, and a nodule followed for two years without change is considered benign (\*exception being the completely ground glass opacity that needs to be followed for a longer period of time). Consequent to this definition of “benign”, the number of “positive” findings falls in the third year of NLST screening (T2) from an average of >27% of all screened CTs during the baseline and first year follow-ups (T0, T1) to under 17% (16.8%) during T2 when nearly one-third of previously “positive” NCNs were relegated to a stable and hence “negative” category. Consequently, the overall positive screening test rate of 24.2% is lower than the T0 and T1 screen positive rates.

Even though the NELSON trial, another large multi-national randomized control trial of CT screening for lung cancer, is on-going and the final data are not ready for analysis, it is important to mention a variance in the definition of “positive” and also of the methods of analysis compared to the NLST trial. In this European study of high-risk subjects randomized to CT versus no screening by any modality, measurements are performed using a volumetric analysis with a lower limit of 50 mm<sup>3</sup> (NCN of 4.6 mm diameter) below which nodules are considered “negative”.<sup>36</sup> A “positive” classification is assigned to nodules of > 500 mm<sup>3</sup> (>9.8 mm diameter assuming a perfect spherical configuration), with nodules in between these two cut-points labeled as “indeterminate”. Using this definition, the majority of non-negative NCNs found by CT screening will fall into this indeterminate category. By having an “indeterminate nodule”



category, the baseline screening prevalence of lung cancer (2.6%) is not significantly different from NLST and other CT screening studies, but the proportion of incident lung cancer in the “positive screen” category on follow-up will increase, and fewer NCNs will change from “positive” to “negative” categorization.

The first step of follow-up for almost all “positive” NCNs, categorized by whichever methodology, will be additional imaging studies. Nonetheless, a variety of approaches are available and comparative assessments have not been carried out. Additionally, the protocols tested, e.g. NLST, are not specific to people with underlying lung disease including COPD.

A standard recommendation and a “best practice” is for the evaluation of suspicious and of indeterminate pulmonary nodules to be performed by an interested and collaborating multi-disciplinary team of physicians and ancillary health care personnel with expertise in the area of thoracic malignancies. The team should include diagnostic and interventional radiologists, nuclear medicine experts (nuclear metabolic imaging), pulmonologists, thoracic surgeons, oncologists and radiation oncologists.

Although this “best practice” recommendation for patients being evaluated for the diagnosis and staging of suspected lung cancer is uniformly endorsed by key opinion leaders and the major medical societies involved in research and clinical care (IASLC, ACCP, NCCN), the infrastructure for multi-disciplinary thoracic-oncology tumor boards and clinics is not uniformly in place at present.

### **3.5 Identification of smokers at high risk for lung cancer**

Another key issue is deciding who is considered sufficiently high-risk to warrant screening with appropriate cost-benefit considerations and meaningful reduction of lung cancer mortality. For lung cancer, smokers have greatly increased risk compared to never smokers. However, for a screening strategy for lung cancer, it would be useful to have tools that identify those smokers at highest risk. Many analyses have explored the quantitative relationships between measures of smoking and lung cancer risk. These analyses have shown the importance of duration of smoking, number of cigarettes smoked, and, for former smokers, the time since quitting. A landmark analysis of the data from the cohort study of British physicians showed that duration of smoking and numbers of cigarettes smoked have quantitatively distinct effects on lung cancer risk and that they should not be combined for estimating lung cancer risk.<sup>70</sup> Further information on the quantitative relationships of measures of smoking with lung cancer risk can be found in the comprehensive review in the 2004 monograph from the International Agency for Research on Cancer (IARC) and the 2004 report of the US Surgeon General.<sup>71,72</sup>

More recently, predictive models have been developed that estimate the probability that lung cancer will occur during specified time intervals. Such models are of particular interest for risk stratification in order to identify candidates for screening. The development and use of prediction models parallels the approach taken for breast cancer; a risk-factor based model, the “Gail model” has long been available.<sup>73</sup> The model’s predictions are used for a variety of purposes, including informing patients of their potential risk, guiding screening, and selecting women for clinical trials.

Three prediction models for lung cancer are now available: the “Bach model” based on data from the  $\beta$ -Carotene and Retinol Efficacy Trial (CARET), the “Spitz model” based on data from an ongoing case-control study, and the Liverpool Lung Project based on a case-control study in

Liverpool, England.<sup>74–76</sup> The general approach used to develop the models is similar. The epidemiological data are analyzed to identify risk factors and estimate the associated relative risk. The relative risk estimates are then used to project risk over time. Various statistical approaches are used to identify the most informative variables and to validate the final model. The measure of prediction used is generally the area under the curve (AUC) from receiver-operating characteristic (ROC) analysis; the AUC varies from 0 to 1.0, from no predictive value to perfect prediction.

D’Amelio and colleagues compared the performance of the three models in an independent data set, a case-control study carried out in Boston.<sup>77</sup> Etzel and Bach also provide a useful comparison of the three models.<sup>78</sup> The AUC values for the models range from about 0.60 to 0.70. The AUC values for the Spitz and Liverpool Lung Project models were 0.69 while that for the Bach model was 0.66. Spitz and colleagues have refined the original model in two ways: 1) by adding two markers of DNA repair capacity with a slight gain in AUC<sup>79</sup>; and 2) developing a model specifically for African Americans, which performed better than the model based on whites in this racial group.<sup>80</sup>

Undoubtedly, these models will continue to be refined; their predictive power may be greatly enhanced if additional genes determining risk for cancer in smokers are identified. For now, they provide a tool for risk stratification, but lack the sensitivity and specificity needed for managing individual patients and advising them on screening.

### **3.6 Cost-effectiveness overall and for subgroups**

One measure of the programmatic value of a screening test is its cost-effectiveness, that is, how do the costs compare to the effectiveness of the test. Cost-effectiveness is often estimated by modeling the events of persons who undergo alternative diagnostic or treatment strategies and cumulating the costs that are accrued with different interventions. For the example of the NLST, a cost-effectiveness model would consider efficacy and the costs (including not only screening costs, but the costs of work-up and therapy received subsequently) of a screening program. In a comparative cost-effectiveness analysis, several alternative approaches would be compared. Mahadevia provides one example of a cost-effectiveness study of helical CT screening that was performed before the NLST was completed.<sup>81</sup>

There are several key determinants that need to be taken into account in defining the cost-effectiveness of a lung cancer screening program:

- First, a CT screening program for lung cancer should be compared to other possible lung cancer prevention and treatment strategies. This comparison includes prevention of cancer through smoking cessation programs, as well as, usual medical care. Smoking cessation programs have been shown to be cost-effective and to have an appropriate cost-effectiveness ratio.
- Second, the characteristics of persons who would undergo screening should be anticipated, including the age at first screening, smoking history (with regard to dose, current and former smoking status), comorbid disease status including factors that would affect the prognosis associated with testing and treatment such as lung function level and cardiovascular disease status.
- Third, the characteristics of lung cancer occurrence in the screened population including the incidence and the distribution of lung cancer types—adenocarcinoma, squamous cell carcinoma, small cell carcinoma.

- Fourth, one of the most important determinants is the proportion of cancers that are detected at advanced versus early stage. This is often referred to as “stage shift” and it is the fundamental intermediate outcome that will affect mortality.
- Fifth, the harms from testing and treatment include the complications of more invasive testing and treatment including bronchoscopy, surgery, radiation, chemotherapy and psychological stress associated with false positive labeling.
- Sixth, there are many costs that need to be considered including the upfront cost of screening examinations performed on an annual basis and downstream costs of further diagnostic testing, treatment of cancer detected including hospital, physician care and pharmacologic therapy and caregiving. It is important to recognize that screening may also avert costs associated with intensive treatment of terminal cancer.
- Seventh, adherence to a screening program is often less complete in routine clinical practice than in research studies and this reduced adherence impedes the realized effectiveness of a program.
- Eighth, the quality of life associated with various states of health along the continuum of lung cancer (e.g., being screened, living with indeterminate disease, living with lung cancer, and being treated for lung cancer) must be considered.

### **3.7 The Impact on Lung Cancer Screening on Quality-of-Life**

Screening for lung cancer has the potential to have both positive and negative impacts on patients’ lives, independent of any direct discomfort or physical risk associated with the screening procedure.<sup>82</sup> For example, screening might potentially reduce anxiety and improve quality of life for patients who learn they do not have lung cancer. Patients for whom screening identifies cancers that are treated successfully might not only gain additional years of life, but years of life with enhanced quality of life. Conversely, uncertain screening results or false positive tests could result in increased emotional distress and fear. Patients with screening-detected cancer that left untreated, would not have reduced the number of years of life, are at risk of experiencing the negative impact of cancer treatment on quality of life, as well as the additional burden of the anxiety associated with a cancer diagnosis.

A limited number of studies have examined the impact of lung cancer screening on patient’s emotional response or quality of life. Vierikko examined the psychological impact of CT screening for lung cancer and occupational pulmonary disease among asbestos-exposed workers.<sup>83</sup> Overall health anxiety was found to be significantly reduced after screening, and after one year no significant psychological impact was observed between those who received additional examinations or testing because of positive screening results. Van den Bergh et al. measured changes over time in health related quality of life (HRQoL) and anxiety among 733 participants in the Nelson lung cancer screening study.<sup>84</sup> They found no clinically relevant changes over time in anxiety or HRQoL, however, a measure of lung cancer-specific distress (Impact of Event Scale) did find clinically significant increases in distress immediately after an indeterminate test result and a significant decrease in distress after a negative result. In a meta-analysis of 12 screening studies that examined the adverse short and long-term psychological impact of screening (6 of which involved cancer), Collins concluded that screening does not appear to have long-term (greater than 4 weeks) negative emotional impact and too few studies have examined short-term impact.<sup>85</sup>

In summary, the limited evidence to date does not suggest that lung cancer screening significantly impact patients’ quality of life or emotional well-being. However, the pending results from the NLST quality of life sub-study will provide important clarification on the short-

and long-term impact of CT screening on quality of life.

### **3.7 Radiation Risk**

Spiral CT scans involve exposure to ionizing radiation, a known cause of cancer. In addition to the lung, lymph nodes and other structures are within the field; and for women, the breasts are also irradiated during scanning. The quantitative risk of cancer associated with radiation has been characterized with reasonable certainty, primarily on the basis of the long-term epidemiological study of the atomic bomb survivors in Japan. This study, along with other epidemiological studies and experimental findings, shows that radiation risks are linear with dose and without a threshold below which there is no risk. The risk for radiation-related cancer typically begins about two decades following exposure.

Thus, any consideration of the risks and benefits of CT screening needs to consider and calculate the potential for the radiation exposure from screening to cause cancer. The burden of excess cancer will depend on the age distribution of the screened population, mortality patterns, and possibly increased susceptibility to radiation-caused lung cancer among smokers. Such calculations are in process now by the National Cancer Institute. We note that radiation doses should drop in the future with newer technology and greater consideration of the imaging dose.

## **4. How can these uncertainties be addressed?**

### **4.1 Further analyses of NLST participants**

To date, only the main NLST results have been reported. Papers are anticipated that will further detail the findings with regard to quality-of-life, diagnostic work-up and complications. In order for the ALA to address the concerns of its constituents, findings in relation to level of FEV<sub>1</sub> and presence of COPD will be of particular interest. This panel recommends that a request be made to the NLST investigators to obtain information on study participants with regard to the distribution of lung function and the presence of lung disease, clinically diagnosed or present on CT. For the purpose of providing guidance and developing population models, the rates of various complications during work-up and surgical treatment in relation to underlying lung disease are of great interest.

There is a master project list of topics of potential interest based on data collected from the longitudinal NLST that is slated for follow-up analysis and for future publication. Items on the list include validation of existing and development of additional lung cancer prediction model(s), CT scoring of emphysema, correlation of the longitudinal changes in pulmonary function with the longitudinal changes in the CT scans or chest x-rays and the diagnosis of lung cancer, cardiac and other vascular findings, and extra-thoracic findings. Another important area awaiting analysis is whether CT screening and results affect rates of smoking cessation - and of relapse- and quality of life issues depending on screening modality and findings.

As an integral part of the NLST study, future analyses for promising lung cancer biomarkers was anticipated by the prospective collection of serial specimens of blood, urine, and sputum collected from a total of 10,208 participants at 15 screening centers participating in the NLST. Specific proposals for biomarkers to be studied and choice of candidate biomarkers should be determined by an independent scientific panel.

## 4.2 Population Modeling

Because one study, including the NLST, cannot address all the uncertainties when a screening program is implemented over a long time frame, population modeling of the potential effects under certain assumptions is a useful tool for assisting in making resource allocation decisions. These models using probabilistic principles and forecasting techniques (e.g. Markov and simulation models) can incorporate the best evidence regarding the many variables that a screening program can entail. Population benefits, harms and costs can be modeled. These include frequency of screening, adherence screening, cost of screening and response to treatment, to name a few.

Sensitivity analysis, a technique that computes benefits, harms or costs for a range of possible estimates of many parameters can narrow disagreements between screening advocates and opponents to a few key parameters. For example, if there are differences in the prevalence or outcomes of COPD among populations considered for screening, one can see how much this affects the effectiveness of the screening program. It would be useful to consider population modeling for entities deciding on use of helical CT for screening.

From the perspective of the ALA, models should:

- Model lung cancer risk and complication rates by pulmonary disease characteristics (e.g. level of lung function)
- Reflect the increased risk for lung cancer associated with COPD
- Incorporate risks for work-up of nodules in people with COPD of varying degrees of severity.

## 5. Specific Recommendations

The committee offers its interim recommendations in **bold**. The committee recognizes that recommendations released by other organizations may differ from those below. However, as recommendations from other organizations will also be based on the best available scientific evidence, the committee is confident that there will be more similarities than differences from recommendations from various groups.

The NLST is the first optimally designed clinical trial to show that screening for lung cancer with a low-dose CT scan reduces mortality among a high-risk population. The American Lung Association Lung Cancer Screening Committee acknowledges that the findings from the NLST trial are conclusive and that the results provides promising hope for lung cancer mortality reduction for those individuals at the *highest risk* for lung cancer. **Therefore, the committee recommends that the ALA support low-dose CT screening for those people who meet the criteria for the NLST: current or former smokers (defined as those who quit within the last 15 years), aged 55 to 74 years, with a smoking history of at least 30 pack-years and no history of lung cancer. For those who chose to undergo the screening process, smoking cessation should be continuously emphasized as it remains the best method of reducing lung cancer risk. Additionally, the committee recommends that the ALA advise against the use of chest X-rays for lung cancer screening.**

Many questions remain, however, as to the optimal method of and the effectiveness of low-dose CT screenings in the general population and in other high risk groups not included in the NLST study such as younger age groups that already have 30 pack years of smoking. Additionally, these findings have not yet been reported in a way that would guide recommendations specific to people with COPD, a key constituency for the ALA. Nor is there evidence at this time that all current and former smokers or

never smokers exposed to second-hand smoke should be screened by CT. ***Therefore, the committee cannot recommend universal lung cancer screening at this time and reiterates that smoking cessation is still the best method of reducing lung cancer risk among those who smoke. This recommendation should be re-evaluated as further evidence becomes available.***

As the ALA is responsible for providing guidance to, and on behalf, of the public on issues affecting lung health, the Committee understands that something must be done to assist individual patients and their health care providers in discussions regarding primary and secondary prevention of lung cancer i.e. smoking cessation and low-dose CT screening. The committee acknowledges the challenge inherent in communicating the complicated trade-offs involved in making a decision to undergo lung cancer screening. The choice to undergo lung cancer screening must be an individual one and the ALA should ensure that every patient has the information they need to make an informed decision. Patients should be informed beforehand about possible increased risk of radiation exposure, all possible follow-up procedures in the event of an abnormal finding, and the risks and costs of such procedures. Patients should be informed beforehand that a negative (without abnormalities) low-dose CT screen does not guarantee that they will never have lung cancer. ***Therefore, the committee recommends that the ALA develop a toolkit which will provide a comprehensive framework on the lung cancer screening process, outlining the potential benefits, risks, costs (emotional, physical and economic) of lung cancer screening to assist people with lung disease, particularly COPD, in discussions with their pulmonologist or other knowledgeable physician regarding the advisability of low-dose CT screening in the context of the severity of their disease. This toolkit should be presented in the language and format appropriate to a broad range of backgrounds. Appendix 1 has toolkit materials based on the committee's feedback.***

Because lung cancer CT screening is not currently covered by Medicare or private insurers, using low-cost or even free screenings to recruit patients, without providing guidance about potential complications and costs, is not advised. Similarly, direct-to-consumer advertising to recruit patients who might have resources to pay out-of-pocket for low-dose CT screening and the potential to produce revenues with follow up procedures, without including at the same time information about risks and costs, does not only discriminate against those without such resources, but may call into question the best interests of the communities being served. Finally, the promotion of such services should not prey upon the public's fear of lung cancer while leading them to believe that low-dose CT screening will eliminate all risk from lung cancer. ***Therefore the committee recommends that ALA should call upon all hospitals and screening centers to establish ethical policies for advertising and promoting lung cancer screening with low-dose CT, as well as, call upon all hospitals and screening centers to use this opportunity to fully educate the public about lung cancer, its risks and prevention, and the importance of careful and thoughtful discussions between patients and their physicians.***

***Lastly, the committee recommends that the ALA strongly advocates for screening to be linked to access to "best practice" multidisciplinary teams that can provide the needed follow-up for evaluation of nodules.*** While many facilities may not have such expertise on site, the institutions carrying out the screening should be able to make referrals to appropriate institutions. The best results will most likely occur in institutions with the longest experience in conducting low-dose CT scans, as well as, the latest CT technology.

## **6. Future Endeavors**

The committee acknowledged that other professional medical organizations with an interest in this area are developing a variety of workshop-reports, position papers, recommendations, experts' consensus statements through guidelines on the topic of CT screening for lung cancer. These include, but are not

limited to, the US Preventive Services Task Force (USPSTF), American College of Chest Physicians (ACCP), National Cancer Care Network (NCCN) and American Society of Clinical Oncology (ASCO). As noted that the International Association for the Study of Lung Cancer (IASLC)<sup>4</sup> and the American Cancer Society<sup>3</sup>, have already published a workshop-report and interim guidelines, respectively. In general, they will have similar common goals that include:

- Identification of high risk individuals for lung cancer CT screening programs
- Developing radiological guidelines for use in developing screening programs
- Developing guidelines for the clinical evaluation of the “indeterminate lung nodules” found on CT screening
- Making recommendations for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening
- Developing guidelines for pathology reporting of nodules from LCCT screening programs
- Integrating smoking cessation into future LCCT screening programs.

In future years, additional modalities may be available to enhance the predictive accuracy of follow-up protocols. These tests are generally non-invasive: breath analysis, either of volatile organic compounds (VOCs) profiles or of exhaled breath condensates that can measure larger compounds including peptides.<sup>86-88</sup> Sputum analysis, not for standard cytologic diagnosis of low sensitivity, but for morphometric or volumetric 3D “malignancy associated changes” is under evaluation. Additional tools potentially include cutaneous bioconductance measurements that may detect altered bioimpedance properties of a malignant intra-thoracic lesion and minimally invasive assessments including blood tests for circulating DNA, tumor cells, tumor associated autoantibodies, and a host of cancer associated molecular biomarkers.<sup>89-91</sup> Some of these studies may be performed independently (blood tests and nasal swabs to test nasal epithelium), while others may test cells that are otherwise “non-diagnostic” that are acquired during other tissue sampling procedures (cytologically normal sputum, bronchial epithelium) to look for genomic profiling or morphologic changes that are epiphenomena strongly associated with lung cancer development and progression.<sup>92,93</sup> These treatment-enabling technologies are not considered “diagnostic” by themselves, but they may prove useful for estimating the pre-test or prior probability that lung cancer is present in a particular individual. To date, none of these tests have reached a satisfactory state of validation to warrant their routine clinical use (even though several serum based tests are being marketed based on CLIA certification), their parallel development will likely produce “companion diagnostic” tests that may be useful as part of the assessment of the indeterminate lung nodule. Additionally, PET scanning will probably also be used in the future for differentiating malignant from non-malignant nodules.

There was discussion by the committee as to whether a second report should be developed focusing on stakeholders such as the medical community, insurance companies and government agencies. It would involve population modeling of currently unpublished data collect as part of the NLST trial, cost-benefit analyses and the development of risk-prediction tools. The future report would also benefit from further analyses of the NLST data, directed at:

- Clinical Report Forms
- Diagnostic yield by emphysema scoring
- Availability of Quality of Life measures
- Quit rates/smoking cessation by screening status
- Differences in outcome among subgroups

If a second report is commissioned by the ALA, members with policy expertise will be recruited.

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## **Making an Individual Decision to Get Screened:**

### ❖ **Understanding**

- Are you considered high risk for lung cancer?
  - NLST high risk group
  - Genetics
  - Smoking History – pack years
  - Other exposures – occupational, etc.
- What is your current health status? Do you have co-morbidities like COPD?
- What are my screening options? (Physician should eliminate chest X-rays)
- What does the screening process entail? (Physician to use ALA Flow Chart)
- Where should I go for a CT scan?

### ❖ **Risks**

- What are some of the complications of the diagnosis procedure?
  - False Positives
  - Negative results do not absolutely rule out the chance for cancer incidence
- What is the cumulative exposure to radiation?
- What are the unknowns?

### ❖ **Costs**

- Does my health insurance company reimburse for CT scans?
- How much does a CT scan cost? What about the cost of follow up procedures?
- How will screening affect my quality of life? (living with indeterminate diagnosis)
- How much time and personal costs will I spend throughout the screening process?

# Should my patient be screened?

## ❖ Prior to appointment: Questions to think about

- Does my patient meet the NLST criteria or another high-risk profile that makes them good candidates for screening?
- What were the NLST results? 20% lung cancer reduction
- What are the benefits/risks for my patient if screened?
- What are my referral options? Where do I refer?

## ❖ During the average medical visit: ~12 minutes

- Take a complete health history and determine possible co-morbidities (conduct spirometry?)
- Advocate smoking cessation
- Educate about symptoms of underlying lung disease
- Discuss the benefits /risks and possible procedures associated with the screening process (Use ALA Flow Chart)
- Discuss costs of screening – health insurance reimbursement, time and personal costs
- If recommending screening, discuss
  - Availability – low dose CT is available and will be done, high quality machine and staff
  - Low Dose CT /qualified center with expertise to follow up after test
  - Follow up care through multidisciplinary approach.

## ❖ Points to Remember:

- Do not offer a Chest X-ray as an option for screening
- Refer patients only to qualified centers, those providing low-dose CT scans and a multi-disciplinary team for follow-up
- Ensure that patients know the difference between a screening test and screening process.

# Figure 1: What Happens If I Choose to Be Screened?

