Providing Guidance on Lung Cancer Screening to Patients and Physicians

An Update from the American Lung Association Lung Cancer Screening Committee
April 30, 2015

Executive Summary

Lung cancer kills more men and women than any other type of cancer. For 2014, it is estimated that more than 159,000 Americans will die of lung cancer, accounting for approximately 27 percent of all cancer deaths. Of all cancers, lung cancer has one of the lowest five-year survival rates at only 17.8 percent. A strategic imperative of the American Lung Association is to "defeat lung cancer" and the American Lung Association has great interest in reducing the morbidity and mortality associated with this lethal disease.

Screening for individuals at high risk has the potential to dramatically improve lung cancer survival rates by finding the disease at an earlier, more treatable stage. 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. In response to these exciting results, the Lung Association convened a committee chaired by Jonathan Samet, MD, MS to review current scientific evidence and assist the Lung Association in offering the best possible guidance to the public and those suffering from lung disease. The report was one of the first from a voluntary health organization and was widely disseminated and well received.

Since 2012, there have been many important changes to the lung cancer screening environment. In December 2013, the United States Preventive Services Task Force (USPSTF) gave use of LDCT for lung cancer screening a "B" recommendation, which means that under the Affordable Care Act, most people meeting the criteria will now have private insurance coverage without co-payments of other barriers. This was followed by a similar decision by the Centers for Medicare and Medicaid Services (CMS) in February 2015 to cover screening for a similar (although not congruent) at-risk population.

Given these new lung cancer screening recommendations, the emergence of new evidence and accumulating experience with screening, as well as concerns with regard to the optimal implementation of screening programs, the Lung Association's scientific leadership concluded that the March 2012 report should be updated in order to assure the organization is acting and communicating based on the most recent evidence. The new report reviewed key publications based on the NLST as well as those from other clinical trials and other studies published since the first report, with the goal of presenting evidence-based guidance to patients and physicians. The committee reviewed evidence on false positives, overdiagnosis, patient anxieties, screening implementation refinements, complication rates for the screening population and the cost-effectiveness of LDCT. Topics not covered in the first report include a discussion of smoking cessation in the context of screening as well as guidance specific to people with chronic obstructive pulmonary disease (COPD), a key constituency for the Lung Association.

After a comprehensive review of the literature that has been published since the initial report, the subcommittee makes the following recommendations:

- The Subcommittee reaffirms that the evidence from the NLST supports the implementation of lung cancer screening for high-risk individuals via LDCT. Experience to date also validates the

Subcommittee's prior recommendations around institutional approaches to lung cancer screening, including the need for the availability of multidisciplinary clinical teams.

- Assessment of smoking and the provision of smoking cessation services must be part of any lung cancer screening program. Research is urgently needed to develop approaches that will maximize cessation rates among smokers undergoing screening.

- Present criteria for selecting candidates for LDCT largely follow the entry criteria of the NLST, e.g., those from the USPSTF and from CMS. The Subcommittee agrees that these criteria should be the starting point, but recommends that research should be carried out to support the development of risk-based criteria. While acknowledging that these criteria have implications for insurance coverage, the key clinical determinants of the appropriateness of screening include the underlying risk for lung cancer based on smoking history and age, as well as on health status and the potential risks of diagnostic work-up and treatment. The arbitrary age and smoking history criteria may not fit well with all clinical situations, e.g., a 50 year-old smoker with a 60-pack-year smoking history, and consequently the subcommittee urges that patients and their physicians carefully review risks and benefits with attention to the specifics of each person making a decision about screening. Accessible and patient-friendly risk prediction tools are needed to support decision-making. Data gathered on those receiving screening will be extremely useful for developing predictive models that will cover common clinical scenarios.

- Systematic data collection is requisite, and should cover detection of COPD and evidence of coronary artery disease. One model system has already been developed for that purpose— LungRADS.

- Gaps in evidence remain with regard to use of LDCT for lung cancer screening, extending across the full screening process. We recommend that a strategic research agenda be developed by a multi-stakeholder group to address the gaps; this is an opportunity for the Lung Association to assume leadership.

- LDCT for lung cancer may also identify previously undiagnosed COPD, given the smoking histories of those eligible for screening. Follow-up lung function testing should be incorporated into protocols, and executed before any invasive work-up approaches are carried out.

- The Lung Association should develop a "Shared Decision-Making" toolkit(s) that would act as a "consumers' guide" for those considering lung cancer screening. The toolkit(s) should cover the following and be evaluated over time:
  o First time screening subject
    ▪ Guidance on selecting a particular institution as the venue for CT screening
    ▪ Indicators of program comprehensiveness and quality
    ▪ Eligibility criteria associated with coverage
    ▪ Results of scan and next steps
      • What is a pulmonary nodule?
      • What if they find a pulmonary nodule on my CT scan?
      • What if they find evidence of COPD?
      • What questions should I ask?
    ▪ Screening candidates that are current smokers –
      • Providing information on how smoking cessation would enhance health outcomes beyond lung cancer
      • Emphasize resources to aid with smoking cessation
  o Returning screening subject for annual repeat screen

- Reviewing new developments over previous year
- Eligibility criteria associated with coverage

Our hope is that this new report will support the Lung Association's mission and help serve as the basis for additional public health education the Lung Association provides on this issue. We encourage the Lung Association to continue to offer comprehensive guidance to the at-risk population, and undertake periodic reviews of these recommendations, as evidence continues to be accumulated.

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I. Introduction

Lung Cancer kills more men and women than any other type of cancer. For 2014, it is estimated that more than 159,000 Americans will die of lung cancer, accounting for approximately 27 percent of all cancer deaths.[1] Lung cancer is also the second most commonly diagnosed cancer in both men and women, second to prostate cancer and breast cancer, respectively, with an estimated 224,000 new cases anticipated to be diagnosed in 2014. Despite this huge and still increasing burden of morbidity and premature mortality, methods for detecting this aggressive disease in its early stages and for treating it effectively have been limited, such that only about 17 percent of current patients will live five years or longer after being diagnosed.[2]

Early detection of lung cancer has now emerged as an effective way to improve the outcome for smokers at high risk for lung cancer and thereby reduce the lung cancer burden. Consequently, there is a need to implement screening as part of a comprehensive clinical and preventive strategy to reduce the frequency of untreatable lung cancer and significantly improve the low survival rates. A clinical strategy for lung cancer that has shown efficacy in a clinical trial is screening with low-dose computed tomography (LDCT). The purpose of a LDCT screening test is to identify early stage lung cancer in an asymptomatic individual and intervene sufficiently early so that a more favorable prognosis is achieved, than if diagnosis had awaited the occurrence of the symptoms and signs that accompany more advanced disease. In August 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 LDCT or standard chest x-ray.[3] The study found that screening individuals with LDCT scanning reduced lung cancer mortality by 20 percent compared to chest x-ray.

In response to the NLST findings, the American Lung Association (ALA), under the auspices of the ALA's Scientific Advisory Committee, convened an expert panel, chaired by Jonathan Samet, MD, MS to review the then available scientific evidence on lung cancer screening in order to assist the Lung Association in offering the best possible guidance to the public and to those at high risk for lung cancer. The report "Providing Guidance on Lung Cancer Screening to Patients and their Families" was released in March 2012; it provided a comprehensive history of lung cancer screening research trials from the 1950s to the NLST and explored a variety of issues relevant to the ALA's constituency, culminating in the following recommendations:

- *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.*
- *Emphasize the need for smoking cessation consultation at numerous points in the screening process as it remains the best method of reducing lung cancer risk.*
- *Advise against the use of chest X-rays for lung cancer screening.*
- *Advise against universal lung cancer screening. Instead it should be reiterated that smoking cessation is still the best method of reducing lung cancer risk among those who smoke.*

- *Develop a toolkit providing 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 in discussions with their pulmonologist or other knowledgeable physician regarding the advisability of LDCT screening in the context of the severity of their disease.*
- *Call upon all hospitals and screening centers to establish ethical policies for advertising and promoting lung cancer screening with LDCT, as well as, 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.*
- *Strongly advocate for screening to be linked to access of "best practice" multidisciplinary teams that can provide the needed follow-up for evaluation of nodules.*

ALA has since joined other notable health organizations and professional societies in calling for lung cancer screening for those individuals who meet NLST criteria and in voicing concerns regarding 1) the exclusion of other high risk groups, and 2) the implementation of LDCT lung cancer screening in the community setting, absent a comprehensive program. The ALA has also been engaged with appropriate members of federal agencies, as well as the Congress, both on its own and as part of LungCAN (The Lung Cancer Action Network), to ensure that CT screening is widely adopted and funded through public and private health insurance. These activities also included participating in and signing on to the Joint Societies[a] consensus document prepared for the Centers of Medicare

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[a] The signatories to this consensus document are a multi-society, multi-disciplinary stakeholders group, including the Lung Cancer Alliance (LCA), American College of Radiology (ACR), The Society of Thoracic Surgeons (STS), The American Association of Physicists in Medicine (AAPM), The Academy of Radiology Research, American Association for Thoracic Surgery (AATS), The American Board of Radiology (ABR), The American Board of Radiology Foundation, American College of Surgeons' Commission on Cancer, American Roentgen Ray Society (ARRS), American Society for Radiation Oncology (ASTRO), Association of University Radiologists (AUR), Blanchard Valley Hospital, Findlay, Ohio, The Fleischner Society, Global Institute of Public Health, New York University, Henry Ford Medical Group, Hollings Cancer Center at the Medical University of South Carolina, Houston Methodist Hospital - Houston Methodist Research Institute Lung Cancer Screening Program, The International Association for the Study of Lung Cancer (IASLC), International Early Lung Cancer Action Program (IELCAP),Lahey Hospital and Medical Center, Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, Massachusetts General Hospital Lung Cancer Screening Program, Montefiore Einstein Center for Cancer Care, National Council of Asian Pacific Islander Physicians (NCAPIP), National Comprehensive Cancer Network (NCCN), National Jewish Health Lung Cancer Screening CT Program, Oakland University William Beaumont School of Medicine, Penn Lung Center of the University of Pennsylvania Health System, Prevent Cancer Foundation, Quantitative Imaging Biomarkers Alliance (QIBA), Radiological Society of North America (RSNA), Society of Chairs of Academic Radiology Departments (SCARD), Society of Computed Body Tomography and Magnetic Resonance (SCBT-MR), Society of Thoracic Radiology (STR), Tobacco Exposure Program at City of Hope Medical Center, The University of Chicago, University of Michigan Comprehensive Cancer Center, Upstate Medical University, and WellStar Medical Group

and Medicaid Services. In advance of their National Coverage Determination decision, this document recommended that the Centers for Medicare & Medicaid Services (CMS) approve coverage of lung cancer screening in high-risk persons by participating providers that meet the practice and quality reporting criteria outlined below and consistent with the ACR LungRADS™ reporting lexicon and Designated Lung Cancer Screening Center designation.

The consensus among professional societies and voluntary health organizations in concluding that LDCT is efficacious for reducing lung cancer deaths has not gone unnoticed by federal agencies. In December 2013, the United States Preventive Services Task Force (USPSTF) gave use of LDCT for lung cancer screening a B recommendation (Definition of a B recommendation: "The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial"). The USPSTF based its recommendation in large part on the results of the NLST, in addition to its review of the results of six randomized clinical screening trials. Under the Affordable Care Act, prevention measures given an A or B grade are included in the Essential Health Benefit, and people meeting the following screening criteria will now have private insurance coverage for screening without co-payments or other barriers beginning January, 2015:
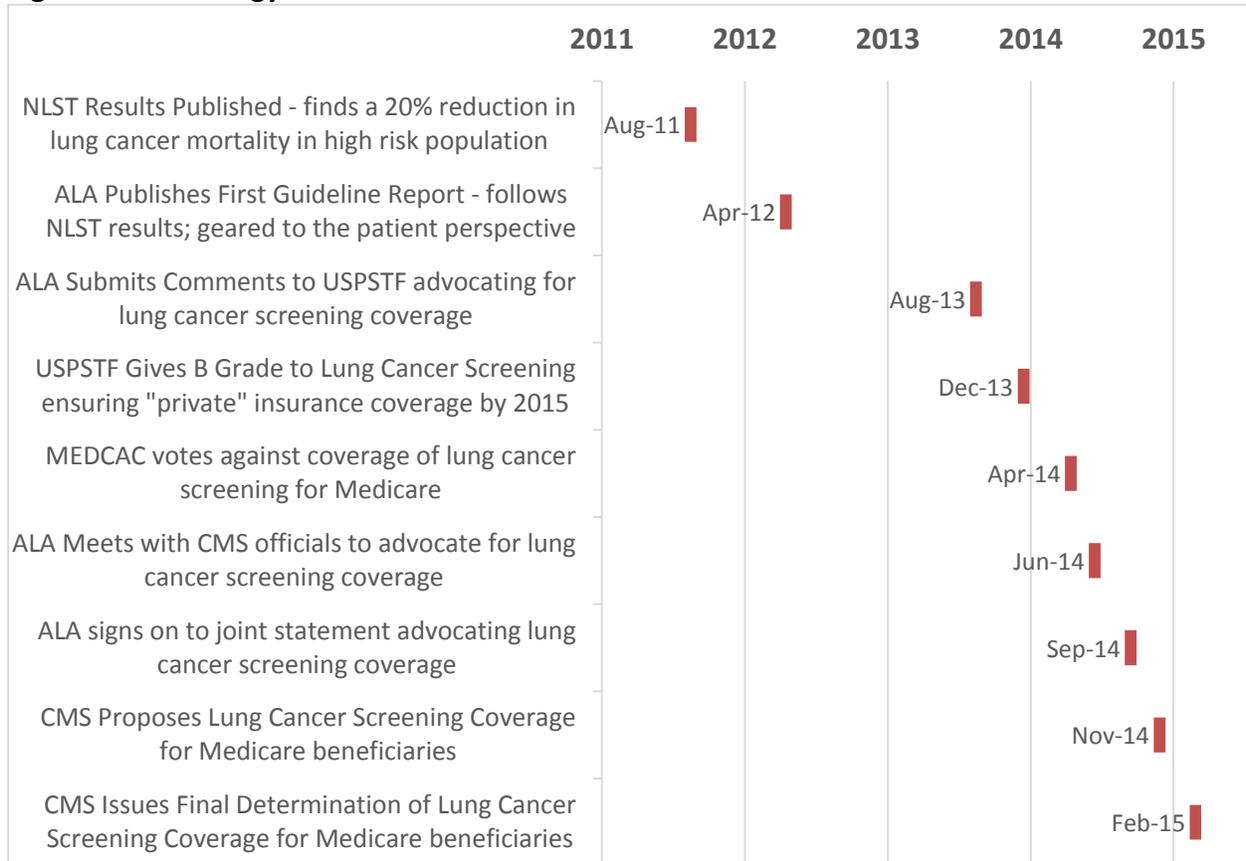
- 55 through 80 years of age
- At least 30 pack-year history of smoking
- Current smokers or former smokers who have quit within the past 15 years

The USPSTF recommendations with regard to the age range for screening (ages 55 to 80 years) differ from the population studied in the NLST (ages 55 to 74 at enrollment). The USPSTF recommendations include current smokers with at least a 30 pack-year history of smoking and former smokers who quit within the last 15 years, following the NLST entry criteria. The Centers for Medicare and Medicaid (CMS) have a separate process to ascertain national coverage determination for new procedures. In November 2014, CMS issued a draft decision regarding low-dose CT lung cancer screening. After a comment period, CMS announced its final coverage determination on February 5, 2015, and coverage for screening began in the designated high risk group immediately. The final determination follows:

- Approved coverage for those 55 to 77 years of age, who have a smoking history of smoking up to 30 pack-years (equivalent of one pack of cigarettes a day for 30 years), currently smoke or who have quit smoking within the last 15 years and have no signs or symptoms of lung cancer.
- Requires smoking cessation counseling or counseling about the importance of quitting and staying quit prior to obtaining approval for a LDCT scan, **as quitting smoking remains the best prevention against the development of lung cancer.**
- Radiologists conducting LDCTs must be certified by an appropriate professional society and have documented training and experience in interpreting lung cancer LDCT scans.
- A prospective registry to collect standardized data on the entire patient experience.

- Requires initial shared decision making consultation but will not require further doctor visits beyond the first screen. Such additional visit requirements would potentially add costs, reduce compliance and unnecessarily burden Medicare, patients, providers and healthcare systems.
- Requires imaging facilities to make smoking cessation available to current smokers.

Figure 1. Chronology of Events

	2011	2012	2013	2014	2015
NLST Results Published - finds a 20% reduction in lung cancer mortality in high risk population	Aug-11				
ALA Publishes First Guideline Report - follows NLST results; geared to the patient perspective		Apr-12			
ALA Submits Comments to USPSTF advocating for lung cancer screening coverage			Aug-13		
USPSTF Gives B Grade to Lung Cancer Screening ensuring "private" insurance coverage by 2015			Dec-13		
MEDCAC votes against coverage of lung cancer screening for Medicare				Apr-14	
ALA Meets with CMS officials to advocate for lung cancer screening coverage				Jun-14	
ALA signs on to joint statement advocating lung cancer screening coverage				Sep-14	
CMS Proposes Lung Cancer Screening Coverage for Medicare beneficiaries				Nov-14	
CMS Issues Final Determination of Lung Cancer Screening Coverage for Medicare beneficiaries					Feb-15

Health care organizations are now turning to developing the best ways to implement screening in the community setting. Since the NLST main results were published in 2011, additional findings have been published related to the optimal implementation of lung cancer screening in the real world and questions have been raised regarding other high-risk groups that might benefit from lung cancer screening. Additionally, equipment and protocols for screening have continued to evolve since the NLST.

Given these new lung cancer screening recommendations, the emergence of new evidence and accumulating experience with screening, as well as concerns with regard to the proper implementation of screening programs, the ALA's scientific leadership concluded that the March, 2012 report should be updated in order to assure the organization is acting and communicating based on the most recent evidence. The goal of this new report is to present the best available

information and evidence-based guidance to patients and their physicians regarding lung cancer screening and to increase public understanding and awareness of LDCT screening for lung cancer. The report is intended to be a guide for the ALA as it fulfills its mission with regard to lung health generally and fighting lung cancer specifically. In preparing this statement, the Committee relied on a systematic review of published English-language reports on lung cancer screening with LDCT from the National Library of Medicine's PubMed database.

Additional topics, not covered in the first report, include a discussion of smoking cessation in the context of screening as well as guidance specific to people with chronic obstructive pulmonary disease (COPD), a key constituency for the ALA. The report is not intended to inform the clinical community regarding best practices as other professional organizations, such as the American College of Radiology and the American Thoracic Society, are releasing guidelines on these topics. Rather, this report provides complementary information and guidance and is intended to focus on communications and information most pertinent to the public generally and to those at high risk for lung cancer specifically.

II. Key Publications since the first report

Since the main NLST results were reported in the *New England Journal of Medicine* in 2011[3], a substantial number of articles have been published using NLST data or data from other clinical trials or patient cohorts assessing LDCT for lung cancer screening. A number of these publications are directly relevant to the objectives of this subcommittee's report.

False Positives and Overdiagnosis

A shortcoming of any screening modality is the possibility that a scan would detect a benign or non-aggressive tumor that would otherwise not have caused any clinical symptoms or progressed to cause death. A retrospective review of a small single arm prospective study conducted in Italy addressed this issue by studying the timing of presentation and growth rate of subsets of non-small cell lung cancer (NSCLC); up to 25 percent of the LDCT detected lung cancers were indolent and represented an over-diagnosis when picked up by LDCT.[4] Furthermore, an analysis of NLST data found that around 18 percent of lung cancer cases, 22.5 percent of NSCLC and 78.9 percent of bronchoalveolar lung cancer cases detected by LDCT were indolent and considered overdiagnosed.[5] The estimate of the rate of over-diagnosis for NSCLC was surprisingly consistent, comparing the large NLST and the smaller Italian study (22.5 percent vs. 25 percent). The authors identify one limitation of their study as the assumption that a high-risk patient will live only 7 years, or the duration of the study. When they modeled the rate of over-diagnosis over the expected lifetime for high-risk patients, the rate of over-diagnosis lowered to 11% with LDCT when compared to no screening and 9% when compared to screening with CXR. The authors found that excluding a diagnosis of bronchoalveolar carcinoma further reduced the lifetime over-diagnosis risk to 2.6%.

The subcommittee noted that many of the false positives seen in the NLST and other studies are actually defined as suspicious nodules. The criteria used within these trials were set to capture as broad a set of findings as possible, so that few actual lung cancers would be missed. Since the

implementation of the NSLT in 2002, research published more recently, algorithms and definitions have been developed that will considerably reduce the percentage of actual false positives found in the screening process. Using the LungRADS algorithm to score findings, the NLST investigators reported a decrease in the false-positive rate in the baseline year from 26.6% to 12.8%. After the baseline year, or during the prevalence screens, which should comprise the majority of screens acquired in a mature program, the NLST investigators reported that the false-positive result rate decreased from 21.8% to 5.3%.

For example, the National Comprehensive Cancer Network (NCCN) developed guidelines that provide recommendations for evaluation of nodules found during screening.[6] If a nodule is detected, clinical follow-up depends on its classification (solid or part-solid, ground glass opacity, gross glass nodule or non-solid nodule) and size. This enhanced definition and evaluation of screening findings and clinical direction should greatly reduce the rate of false positive screens found in clinical practice today. The group at Lahey Hospital and Medical Center demonstrated a reduction in the false-positive rate from 27.6% to 10.6% for baseline screens using ACR LungRADS when compared to structured reporting using the original National Comprehensive Cancer Network's Clinical Practice Guidelines in Oncology: Lung Cancer Screening (version 1.2012), which incorporated positive thresholds modeled after those in the NLST. An increase in false negatives was not found in over 1603 patients with greater than 12-month follow-up. Additionally due to newer and more precise staging classifications, cases are managed differently. The finding of a nodule at screening is now further evaluated based on lesion type (solid or part-solid, ground glass opacity) and size. Tumors of <6mm[m] are no longer operated on, and followed through additional LDCT screens. These and other changes to the management of screening results, in comparison to the NLST approach, should also greatly reduce the rate of overdiagnosis seen in earlier implementation.

These changing strategies should reduce the frequency of adverse events seen in the screening setting of the NLST and other earlier studies. Implementation of screening nationwide, should include consistent use of these new criteria, to reduce both false positives and overdiagnosis. As screening within the recommendations of CMS becomes more widely implemented, additional information on implementation will become available as the experience of those screened becomes part of the established registries and is used to optimize approaches.

Patient Anxieties
Overdiagnosis or a false-positive result may lead to increased costs, anxiety and morbidity associated with diagnosis and cancer treatment. A 2014 report provides findings concerning health-related quality of life and state anxiety in a subset of 2,812 NLST participants who completed standardized instruments at baseline and within 30 and 60 days of being screened.[7] The investigators did not find that a false-positive screen result adversely affected the indexes used, although a true-positive did. Similar findings regarding generic health-related quality of life were reported from the NELSON Trial.[8] Van den Bergh et al. found that two months after receiving screening results, there was no significant difference in generic health-related quality of life for

those participants with an indeterminate or negative result of LDCT screening. However, those participants with an indeterminate result had significantly higher lung cancer-specific distress than those with a negative result (p<0.01).

A small study, a qualitative analysis of 22 patients, also found that responses to indeterminate nodules varied and evolved over time.[9] While all 22 individuals initially feared such a diagnosis, the majority came to accept that the nodule was most likely benign. However a few remained anxious, convinced that the nodule could turn into cancer at any time and should be aggressively monitored for life. The authors stated that patients used results of surveillance tests as well as their own strategies (e.g. vigilance for symptoms, information-seeking, contemplating and controlling modifiable risk factors, avoidance, faith) to manage uncertainty.

Another qualitative analysis of the experience of 19 veterans found similar results. Most experienced mild nodule-related distress with only a few facing severe anxiety.[10] This study found that distress was somewhat mitigated by patients' confidence in their clinician.

The findings of these studies, although small in size, point to the possibility that screening results will affect quality of life. As screening is implemented nationwide and approaches are continually enhanced, there should be ongoing research, both qualitative and quantitative, on any adverse consequences of screening results for well-being.

Screening Criteria Refinements
The most important component of any screening program is the identification of those individuals who would most benefit from the service, in order to minimize the number of false positives. While the NLST employed strict eligibility criteria that relied on age and smoking history only, these criteria were intended to optimize the sensitivity of the trial to test its primary hypothesis. Most scientific experts agree that coverage recommendations should be based on prediction models for lung cancer risk that incorporate the above risk factors and others that might also increase risk in particular individuals, such as occupational history. Additionally, there is a need for full consideration of health status and the potential risks of diagnostic work-up and treatment.[11,12]

Several papers have extended the findings of the NLST to better characterize the performance of LDCT screening in relationship to underlying lung cancer risk. Tammemägi and colleagues developed a new lung cancer risk prediction model, based on participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial.[13] Using participants from the PLCO trial, they compared the performance of CT scanning in detecting lung cancer with two different approaches for selecting screening candidates: 1) application of the original NLST selection criteria; and 2) use of the new PLCO-based risk prediction model to select a population of matching size to that identified with the NLST criteria and at the highest risk levels as predicted by the model. The results showed that the PLCO-based model identified a population among whom test characteristics for CT screening in identifying lung cancer were better than with the NLST criteria. In a separate analysis

of the NLST data, they found that the protective effect of LDCT screening did not vary across risk strata based on the PLCO model.

In another analysis directed at the implications of underlying lung cancer risk for selection of individuals for screening, Kovalchik et al. used the data from the chest radiography control arm of the NLST to develop a lung cancer risk prediction model.[14] This model was then used to stratify participants in the CT arm by predicted risk. From the lowest to the highest risk quintile, the number of false-positives declined and the top three quintiles accounted for 88 percent of the screening-prevented lung cancer deaths. These three quintiles included 64 percent of the participants with false positive results.

Lastly, an analysis of data from two population-based cohorts, the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) and the British Columbia Cancer Agency (BCCA), found that predictive tools based on screenee and nodule characteristics could be used to estimate the probability that lung nodules on baseline screening LDCT scans are malignant.[15] The researchers found that persons of older age, female sex, family history of lung cancer, and emphysema, and larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count and speculation were more likely to have lung cancer.

Together, these analyses reaffirm the need to apply basic principles of screening in developing strategies for using low-dose CT scanning. Valid risk stratification can help to guide selection of candidates for screening; the very strong effect of smoking on lung cancer risk facilitates the development of useful models. The empiric studies done within the NLST, PLCO, PanCan and BCCA study populations need replication in the "real-world" populations undergoing screening in practice.

Effects of LDCT Screening on Tobacco Cessation
Tammemägi and colleagues examined the association between screened detected abnormalities and likelihood of smoking cessation among the current smokers on enrollment (N=15,489).[16] Data from this study suggested that screenees with abnormal, potentially malignant findings are at a "teachable moment" and may be more receptive to recommendations of smoking cessation, hence emphasizing the importance of having smoking cessation resource as a part of an effective screening program. The analysis addressed associations of abnormalities in both trial arms with likelihood of cessation. Overall, the presence of an abnormality was associated with lowered risk of future smoking and the likelihood of continuing to smoke decreased as the category of abnormality worsened.

Cost-Effectiveness of LDCT
A number of studies have indicated that LDCT screening for lung cancer is cost-effective. A cost-utility analysis of lung cancer screening in a cohort of 18 million commercially insured adults aged 50 and 64 with a 30 or more pack-years history of cigarette smoking found that LDCT was highly cost-effective, saving almost 1 million Quality Adjusted Life Years (QALYs). Annual screenings would

cost commercial insurers $27.8 billion over 15 years for screening, diagnosis and treatment, yielding a cost-utility ratio of $28,240 per QALY gained. [17] The authors also claimed that the expected cost of screening and diagnosis was $0.76 per-member-per-month (pmpm) in 2012 dollars versus $2.50 pmpm and $0.95 pmpm for mammography and colorectal screening (2006 dollars), respectively.

An analysis of PanCan data found that the average cost to screen individuals who had two percent or greater risk of lung cancer with LDCT was between $400 and $500 per-person for the initial 18-months of screening following a baseline scan. Average per-person costs for curative surgery were $33,500 compared to $50,000 for chemotherapy and palliative care. As such, treating advanced stage lung cancer was more expensive than both screening and curative intent treatment.[18]

Lastly, analysis of the NLST data found that compared with no screening, screening with LDCT cost an additional $1,631 per person (95% confidence interval [CI], 1,557 to 1,709) and provided an additional 0.0316 life-years per person (95% CI, 0.0154 to 0.0478) and 0.0201 QALYs per person (95% CI, 0.0088 to 0.0314).[19] The corresponding incremental cost-effectiveness ratios were $52,000 per life-year gained and $81,000 per QALY gained but these ratios varied widely in subgroup and sensitivity analyses.

Widespread and effective implementation of a national lung cancer screening program using LDCT is necessary if we are to reduce mortality associated with the leading cause of cancer death in the US. In order to meet these goals, access to good quality centers that can provide LDCT in a standardized approach is required. However, a recent analysis of the growing consortium of centers meeting the Lung Cancer Alliance's (a patient advocacy and lung cancer research consortium) database of "Centers of Excellence" reveals that there are uneven geographic distribution of centers which choose to meet the group's requirements for certification.[20] In fact, the researchers found that the majority of LDCT screening centers were located in the Northeast and East North Central State, but none or few were in high incidence states such as Arkansas, Mississippi, Nevada and Oklahoma. Although this analysis does not show that there are no qualified centers able to deliver efficient lung cancer screening at a high standard in these regions, it raises concern that there may be an uneven quality of care around LDCT screening.

III. Modeling (risks/benefits/outcomes; lung cancer prediction models)

Identification of individuals at high risk for lung cancer
A key issue in lung cancer screening is identifying those considered sufficiently high risk to warrant screening such that the benefit of reduction of lung cancer mortality weighs appropriately against the harms and costs. Overall, smokers have far higher risk for lung cancer compared to never smokers, but screening needs to be reserved for those at particularly high risk, at the least matching the risk level of participants in the NLST. By selecting a population for screening with sufficiently high prior probability of lung cancer, the positive predictive value (likelihood of lung cancer given screen positive) can be optimized so as to minimize potentially costly false-positives.

Thus, in implementing a screening strategy for lung cancer, it would be useful to have tools that identify those smokers at sufficiently increased risk with a high degree of certainty. Indeed recent studies support risk-based targeting for screening.[13,14] Many analyses have explored the quantitative relationships between measures of smoking and lung cancer risk, showing generally the importance of duration of smoking, number of cigarettes smoked, and, for former smokers, the time since quitting.[21] 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 into aggregate measures such as pack-years.[22] 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 83 from the International Agency for Research on Cancer (IARC) and the 2004 and 2014 reports of the US Surgeon General.[23,24]

More recently, predictive models have been developed that estimate the probability that lung cancer will occur in an individual during specified time intervals. Such models are of particular utility for risk stratification in order to identify high-risk candidates for screening and for physicians to use as tools to engage patients in shared decision-making around screening, as well as to provide understanding to their patients of the risks of continuing to smoke. The development and use of prediction models for lung cancer risk mimics the successful approach taken for breast cancer; a risk-factor based model, the "Gail model" has long been available and refined over time.[25] The model's predictions are used for a variety of purposes, including informing patients of their potential breast cancer risk, guiding mammographic screening and selecting women for clinical trials.

Several prediction models for lung cancer are now available (Table 1). Examples are the "Bach model" based on data from the β-Carotene and Retinol Efficacy Trial (CARET), the "Spitz model" based on data from an extensive case-control study of lung cancer and the Liverpool Lung Project based on a case-control study in Liverpool, England.[26–28] The general approach used to develop the models is similar. The epidemiological data are analyzed to identify risk factors and to estimate the associated relative risk. Risk factors considered in the models include age, sex, active smoking history, passive exposure to tobacco smoke (secondhand smoke), family history of cancer, dust exposure, prior respiratory disease (such as COPD), body mass index, education, asbestos exposure history, history of pneumonia and history of cancer other than lung cancer. The relative risk estimates are then used in a life-table to project risk over time. Various statistical approaches are used to identify the most informative variables and to validate the final model in samples other than the derivation sample. 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, i.e., 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.[29] Etzel and Bach also provide a useful comparison of

the three main models.[30] 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; and 2) by developing a model specifically for African Americans, which performed better than the model based on whites in this racial group.[31,32]

As described above, Tammemägi et al. recently modified the 2011 lung-cancer risk-prediction model from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.[33] The AUC was 0.803 in the development data set and 0.797 in the validation data set. The model had high accuracy for predicting the risk of lung cancer over 6 years and was more efficient at identifying persons for lung cancer screening. Raji et al. externally validated the Liverpool Lung Project risk models for 5-year risk of lung cancer using three independent studies from North America and Europe. The AUC was 0.76 in the North American data and 0.67 in the European data.[34]

In addition to the above prediction models, others have been developed for specific ethnic groups including persons of Chinese, Korean and African descent.[35–37]

Table 1. Risk-Prediction Models

Author (publication year)	Study population	Parameters considered in model
Bach et al. (2003)	18,172 subjects, *Carotene and Retinol Efficacy Trial* (CARET) for lung cancer prevention, multi-site, US	Age, sex, asbestos exposure history, smoking history
Spitz et al. (2007)	1,851 lung cancer cases from molecular epidemiology study of lung cancer, 2,001 frequency-matched controls (on age, sex, ethnicity, smoking status), Texas, US	Age, sex, ethnicity, SHS exposure, family history of cancer, dust exposure, prior respiratory disease, smoking history
Cassidy et al. (2008)	579 lung cancer cases, 1,157 age- and sex-matched controls, Liverpool Lung Project, UK	Age, sex, smoking history, family history of lung cancer, occupational exposure to asbestos, prior diagnosis of pneumonia, prior diagnosis of malignant tumor other than lung cancer
Tammemägi et al. (2011a)	70,962 subjects, *Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial* (PLCO), multi-site, US	Age, socioeconomic status, BMI, family history of lung cancer, COPD, recent chest x-ray, smoking history

Tammemägi et al. (2011b)	2,596 subjects, British Columbia Cancer Agency trials, Canada	Age, socioeconomic status, BMI, family history of lung cancer, smoking history, FEV_1, sputum DNA image cytometry
Etzel et al. (2011)	491 African-American cases, 497 age-, sex-, ethnicity-matched controls, 2 sites, Texas, US	Age, sex, smoking history, comorbidities (COPD, asthma, hay fever), environmental exposures (asbestos, wood dusts, etc.), family history of lung cancer or smoking-related cancer
Li et al. (2012)	2,283 lung cancer cases and 2,785 frequency-matched controls (on age, sex, residential area), multi-site, China	Age, sex, smoking history, SNPs (rs2736100, rs402710, rs1051730, rs4083914, rs4488809)
Park et al. (2013)	1,324,804 men in prospective cohort, National Health Insurance Corporation, Korea	Age, smoking history, age at smoking initiation, alcohol use, BMI, physical activity, family history of cancer, fasting glucose levels

Risk prediction models need to be continually refined; their predictive power may be greatly enhanced if additional genetic loci determining risk for cancer in smokers are identified or other biomarkers are identified.[32,38,39] These models provide a tool for risk stratification and possibly for managing individual patients and advising them on screening using shared decision-making around the anticipated risks for particular individuals. As data accumulate from screening programs, such models, generally based on the occurrence of clinically diagnosed lung cancer, can be refined to better predict screen-detected cancers as well as typical clinical cases.

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 clinical pathways and key events for persons who undergo alternative diagnostic or treatment strategies and tallying the costs that are accrued with different interventions. Several measures are considered related to cost-effectiveness, including the cost per year of life saved and cost per quality-adjusted life year (QUALY) gained. In the instance of the NLST and the extension of its findings to high-risk populations, a cost-effectiveness model would consider efficacy and the costs (including not only screening costs, but the costs of work-up and any therapy received subsequently) of a screening program. In a comparative cost-effectiveness analysis, several alternative approaches for lung cancer screening and/or prevention would be compared. Well done cost-effectiveness analyses are important for decision-making as they provide an indication of

future costs and the benefits to be realized and the opportunity for bench-marking against already in-place screening for other diseases.

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

1. A LDCT 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.[17]

2. The characteristics of persons who would undergo screening should be anticipated, including the age at first screening, smoking history (with regard to duration and amount smoked, 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. Accurate risk prediction models may improve targeting and thereby cost-effectiveness.

3. The characteristics of lung cancer occurrence in the screened population including the incidence and the distribution of lung cancer types—adenocarcinoma, squamous cell carcinoma, and small cell carcinoma.

4. One of the most important determinants is the proportion of cancers 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. This stage shift was documented in the follow-up report of the NLST cohort.[40]

5. 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.

6. 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.

7. Adherence to a screening program is often less complete in routine clinical practice than in research studies such as the NLST, and this reduced adherence impedes the realized effectiveness of a program.

8. 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.

9. Sensitivity analyses are needed that examine cost-effectiveness in relationship to reasonable changes in key parameters. Such analyses show how robust findings are to key assumptions and point to areas for research.

10. Benefits may be realized from the detection of undiagnosed coronary heart disease and COPD.

Findings of several cost-effectiveness models were developed before the NLST findings became available[41–44] and several reports have been published since the NLST.[19,45,46] The findings of the analyses have been variable, depending on the approach and the assumptions.

Black et al. carried out a comprehensive, retrospective, cost-effectiveness analysis of screening in the NLST. The analysis compared CT screening to chest radiography and to no screening, drawing directly on the outcomes in the NLST. The results were expressed as the incremental cost-effectiveness ratio (ICER). Compared with no screening, the ICERs were $52,000 per life-year gained and $81,000 per quality-adjusted life-year (QUALY) gained. These figures were in a range that has been judged as reasonable.[19] Black et al. found that cost-effectiveness was more favorable among women than men, among persons with a higher vs lower risk of lung cancer, among current smokers vs former smokers and among older persons vs younger persons. In sensitivity analyses, cost-effectiveness was more favorable when CT screening was considered to affect mortality from all causes and when not all (50 percent) excess lung cancers in the CT group were assumed to be due to over-diagnosis. Cost-effectiveness worsened with inclusion of future health care costs of survivors unrelated to lung cancer, with increased costs of the screening examination, follow-up, and surgery and with a reduction in quality of life related to positive screening results and a diagnosis of stage IA lung cancer.

A series of analyses have been carried out using an underlying life table or actuarial approach. The first antedated the NLST findings.[47] It modeled the costs and benefits for an insured population ages 50-64 years. In the baseline scenario, the cost per life saved was estimated as $19,000 and $26,000 for the highest-cost. The model was extended by Villanti et al. to incorporate the additional benefits of incorporating smoking cessation benefits. A scenario was added based on the NLST results.[17] The addition of smoking cessation improved the cost-effectiveness by between 20 to 45 percent. Finally, Pyenson, using Medicare enrollment, demographics and costs in a similar actuarial analysis estimated that 4.9 million high-risk Medicare beneficiaries (55 to 80 years old with > 30 pack year smoking history and who smoked in the last 15 years) in 2014 would fulfill criteria for lung cancer screening and that screening would cost approximately $1 per member per month.[46] Pyenson concluded that screening was cost-effective at less than 19,000 per life-year saved. Variability in results across analyses arose from differences in assumptions.

These cost-effectiveness analyses, including the analysis of the NLST by Black et al., provide estimates of cost-effectiveness that are commensurate with those for accepted screening tests, such as mammography. The table below compares the $/QALY saved for LDCT screening for lung cancer and other more commonly used public health interventions.[17]

Intervention	Original value	Year	$/QALY saved (2012 USD)
Lung cancer screening with LDCT in high risk population			
Annual screening over 15 years, aged 50–64	$28,240–$47,115	2012 USD	$28,240–$47,115
Other preventive health interventions			
Colonoscopy every 10 years, ages 50–75	$4,870	2008 CAN	$8,552
Annual fecal occult blood screening for colorectal cancer, ages 50–75	$15,991–$18,595	2008 CAN	$28,080–$32,652$31,604–$36,750
Papanicolaou (Pap) test for cervical cancer, every 3 years in women aged 20–65	$11,835	2000 USD	$18,662
Biennial mammography and clinical breast exam in women, aged 50–75 years	$34,000	2000 USD	$53,611
Type 2 diabetes screening, ages 25+	$56,649	1995 USD	$105,650
Annual HIV testing in high risk population	$100,000	2001 USD	$150,745
In-center dialysis vs. no renal replacement therapy	$129,200	2000 USD	$203,724
Cholesterol-lowering medication (statin) vs. Step I diet[a]	$130,000–$260,000	1997 USD	$227,878–$455,755

USD, U.S. dollars; CAN, Canadian dollars.
[a]Among men with LDL> = 160 mg/dL.
doi:10.1371/journal.pone.0071379.t004

Such estimates should be reassuring to health care organizations that are implementing screening programs. However, while a cost-effectiveness evaluation can be very useful in elucidating the determinants of value-based care, especially for payers, such analyses are not directly incorporated in developing guidelines nor in the USPSTF and Medicare coverage decisions. As data accumulate following implementation of screening programs, it will be important for cost-effectiveness to be estimated based on the accruing experience.

In contrast to the findings of the analyses by Black et al. and Pyenson and colleagues, McMahon et al., using a simulation model, found that screening for lung cancer compared to no screening or compared to an annual smoking cessation intervention had unfavorable cost-effectiveness ratios (>$100,000 per QALY gained). Screen participation and ongoing smoking behaviors were taken into account and were found to be important and influential. The analysis did suggest that if screening increased smoking cessation rates 2-fold, the cost-effectiveness was more favorable (<$75,000 per QALY). However, the committee gave greater weight to the analyses reflecting the NLST results.

Interpretation and Conclusions

As they are refined, prediction models for identification of persons who have lung cancer are likely to be of greater utility in targeting persons for lung cancer screening. They have the potential to avoid unnecessary screening, thereby avoiding some of the risks, adverse consequences and costs associated with screening. The use of genetic data in addition to other clinical data has future promise in improving the accuracy of prediction, if sufficiently informative suites of genes are identified. The cost-effectiveness of lung cancer screening varies among studies due to differences in assumptions. Ultimately, actual cost-effectiveness will depend on how screening is implemented in routine practice. Use of prediction models in targeting persons for screening might improve cost-effectiveness.

IV. Complication rates and outcomes for the screening population

One critical issue for the ALA, given its role as a trusted advisor to people with lung disease or at risk for lung disease is to be able to provide information on the risks of lung cancer screening and of the subsequent work-up, given the finding of a nodule. In any screening program, a balance needs to be maintained between the benefits and potential harms of the screening. Reaching this balance requires a well-designed screening protocol that specifies the indications for diagnostic tests as well as for surgical interventions.[48]

One concern is that, when a nodule is initially detected, further diagnostic testing is necessary to further characterize the nodule. This diagnostic testing includes additional imaging or invasive procedures, including transthoracic CT-guided biopsy, transbronchial bronchoscopic biopsy, or a surgical approach. In the NLST, 1.2 percent of patients who had a lung nodule, but not cancer, underwent an invasive procedure such as a needle biopsy or bronchoscopy. Moreover, 0.7 percent of participants without cancer had a thoracoscopy, mediastinoscopy, or thoracotomy.[3] For balance the rate of future thoracotomy for work up of solitary pulmonary nodule is vastly higher—but as suggested, our goal should be as low a number as possible. Again, centers doing screening should track this number and make available that information to individuals contemplating screening at that site along with other relevant site specific outcome results as suggested with the Framework approach endorsed by LCA.

Procedural risks for bronchoscopic transbronchial biopsy are generally low with hemorrhage and pneumothorax being the most common complications. Rates for hemorrhage have been cited as ranging from zero to 23 percent of cases although the hemorrhaging is largely self-limited and major hemorrhage requiring transfusion or hospitalization is rare. Rates of pneumothorax have been reported from one to six percent, although more recent reports indicate a range of one to two percent with only a small proportion requiring chest tube drainage or hospital admission.[49,50] These rates represent overall complication rates, not screening management rates.

Transthoracic biopsy with CT guidance often provides a better chance of diagnostic success in peripheral indeterminate nodules. In a recent report based on administrative data bases from several states, population-based information on rates of complications after transthoracic needle biopsy of a pulmonary nodule were reported.[49] Risks of hemorrhage from CT-guided transthoracic biopsy are reportedly as low as one percent although as many as 18 percent of those developing a hemorrhage require transfusion. The incidence of pneumothorax was approximately 15 percent, although a significant proportion of the biopsies causing pneumothorax required chest tube drainage (6.6 percent of all biopsies). This report also described considerable variation in these complication rates across hospitals and regions in the country.

Unlike minimally invasive biopsy techniques such as transthoracic 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 complete lobectomy and adequate lymph node dissection for staging.[51–54] Thus, the initial surgical approach for the diagnostic portion of the procedure should be as minimally invasive as possible. Video-assisted thoracoscopic surgery (VATS), which is less invasive than thoracotomy, has been associated with lower morbidity rates.[55,56] VATS with limited resection of lung parenchyma, such as segmentectomy or wedge resection, may be better tolerated, particularly in people with lower levels of lung function. However, a surgeon trained in these specialized surgical techniques may not always be available in the general community and screen identified cancer cases should be referred to thoracic surgery centers with appropriate specialized expertise to perform invasive management of screen detected lung cancers.

Nevertheless, diagnostic lobectomies for benign disease pose significant potential morbidity for participants in a lung cancer screening program. Adherence to a screening framework that encourages "best practices" for evaluation of screen-positive LDCT scans can minimize procedures through specific guidelines for follow-up, providing guidance on whether to use follow-up imaging to observe for change over time, obtain a non-surgical biopsy by bronchoscopy or CT-guided transthoracic biopsy or perform a surgical biopsy via VATS wedge resection.[48]

Patients with COPD may have increased risk for complications from some of these procedures. While complications of transbronchial biopsy via bronchoscopy appear comparable between patients with and without COPD,[57] several older reports documented a relationship between level of FEV_1 and risk for pneumothorax.[50] In the population-based study noted above, the presence of COPD was associated with significantly increased risk for all complications: odds ratio (OR) = 1.61;

95 percent 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. Figure 2 shows the risks for complications by age, with adjustment for various predictors including COPD. In particular, patients with moderate to severe COPD may have increased risk for complications, particularly related to surgery.[3,58]

Figure 2: Adjusted Risk for Complications after Transthoracic Needle Biopsy of a Pulmonary Nodule[49]
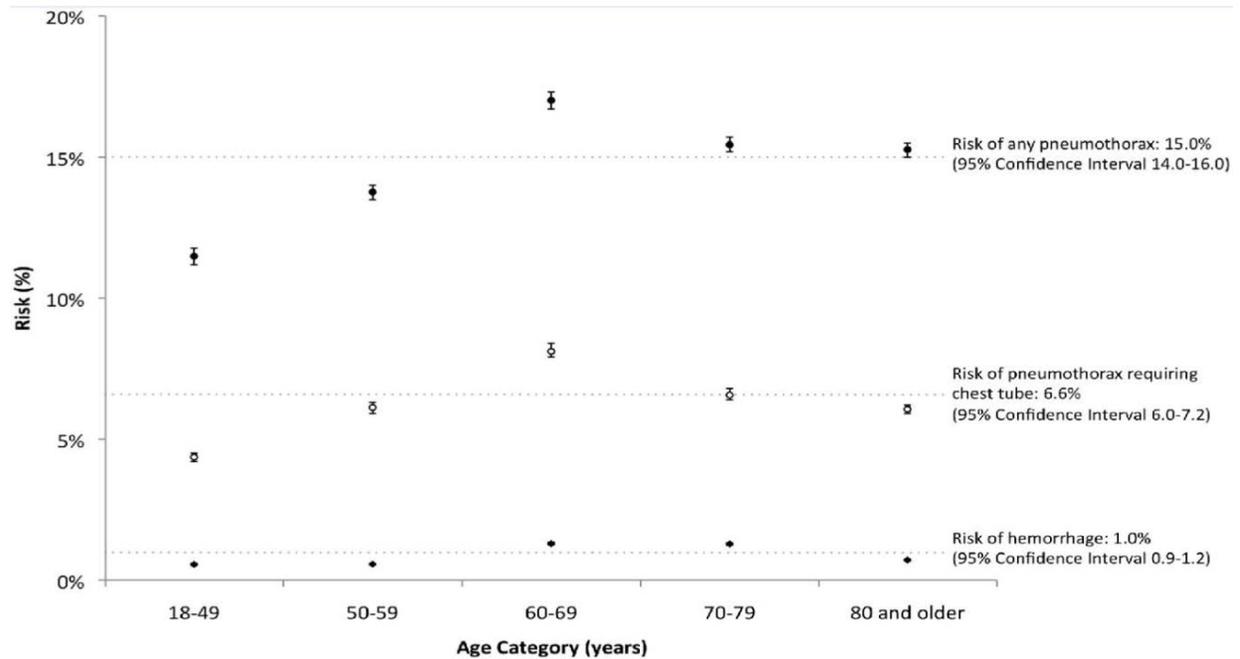
It should be noted that these complication rates for invasive procedures described above are derived from all kinds of cases and not from asymptomatic candidates for screening. In general, screening candidates are healthier with less co-morbidity so procedure rates and operative rates are likely to be less frequent and severe.

V. Clinical Experience to Date

Decentralized Model for Care Delivery: Lahey Hospital and Medical Center
A decentralized model for care delivery distributes CT lung screening responsibilities across appropriate team members and disciplines involved with the program. Here, we draw on the extensive experience gained at one institution to describe the characteristics of such a program. At Lahey Hospital and Medical Center (LHMC), decentralization requires an informed and engaged primary care base to help providers identify the high-risk population. Patient eligibility is re-assessed by trained professionals at the CT screening site. Primary care providers (PCPs) are

preventive care experts who routinely discuss the risks and benefits of a variety of screening choices with their patients. The program helps arm PCPs with knowledge about the NLST results and USPSTF recommendations to support the shared decision making process with high-risk individuals considering enrollment in a lung screening program. Individuals may self-request, but a physician order is required for patient entry into the program. The screening program partners with their PCPs to provide continuing medical education, community outreach patient-centered written materials, integrated smoking cessation, guideline based follow-up recommendations, program navigation support and patient appointment tracking.

Decentralization coupled with a structured reporting system such as ACR Lung-RADS™ controls costs and maintains quality by directing specialist consultation to the relatively few screening cases with suspicious findings (four to five percent) requiring care escalation. At LHMC, these four to five percent of patients have on average a 35-40 percent risk of lung cancer; therefore, primary care is advised to refer those with suspicious findings to pulmonary medicine. After a thorough history and physical, the case is presented through pulmonary medicine or program navigators for review at the weekly multidisciplinary thoracic oncology conference, which is attended by physicians from the departments of pulmonary medicine, pathology, radiology, medical and radiation oncology and thoracic surgery.

Coordination between the multiple stakeholder specialty groups and the Radiology Department is necessary to coordinate patient care on a programmatic level. At LHMC this is overseen by a multi-specialty steering committee comprised of clinical and administration leaders of the various involved specialties. The steering committee joined together to develop the program and now holds bimonthly meetings to provide a common forum to establish consensus, act in concert to overcome barriers to program implementation and create a non-clinical work place for the oncology, primary care and radiology teams to exchange ideas. A radiology working group is charged with managing day-to-day program operations including patient enrollment, exam reporting, results notification and patient tracking as well as reporting program metrics and opportunities for program improvement back to the steering committee. Members of the working group include the supervising radiologist, lead CT technologist, the radiology administrative director, IT personnel and CT lung screening program navigators. All infrastructure and systems developed to manage program implementation were designed in concert by the radiology working group and the steering committee.

Together, the steering committee and radiology working group establish processes for the patient selection, personnel qualifications, follow up system, smoking cessation, equipment, quality control and imaging protocol. A Joint Society Multi-Stakeholder Consensus Document submitted to the Centers for Medicare and Medicaid with signatures from over 70 society and stakeholder groups has endorsed these elements.

http://www.acr.org/~/media/ACR/Documents/PDF/Advocacy/Fed%20Relations/LCS%20Stakeholder%20Letter%2009%2026%2014_FINAL.PDF

http://www.acr.org/Quality-Safety/Lung-Cancer-Screening-Center

Additional resources are listed below:

Patient Selection:
A process for shared decision-making and "on-site" verification of screening eligibility of appropriate high-risk individuals into the screening program must be established.

http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
http://www.brocku.ca/lung-cancer-risk-calculator

Facility/Site Criteria:
The facility/site specifies a system for follow-up, including use of a structured reporting tool and process for reporting quality metrics

http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/LungScreening.pdf

http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Lung%20Screening/Lung%20Cancer%20Screening%20Technical%20Specifications.pdf

http://www.acr.org/Quality-Safety/Resources/LungRADS

Quality Reporting:
http://www.acr.org/~/media/ACR/Documents/PDF/Advocacy/Fed%20Relations/LCS%20Stakeholder%20Letter%2009%2026%2014_FINAL.PDF

Smoking cessation:
http://www.lung.org/stop-smoking/how-to-quit/freedom-from-smoking/

Equipment:
http://www.aapm.org/pubs/CTProtocols/documents/LungCancerScreeningCT.pdf

VI. Smoking Cessation in the Context of Screening
Screening for lung cancer with LDCT scans in the high-risk individuals identified by criteria of the USPSTF has been determined to have benefits that outweigh risks. Based primarily on the findings of the NLST, screening will reduce mortality in those screened, all having extensive smoking histories. While using screening for a primarily preventable disease seems paradoxical, screening offers an opportunity to intervene with those who are smoking at the time of screening. LDCT screening has been found to be cost-effective when compared to other cancer screening protocols. Adding smoking cessation interventions to an annual screening program improves the overall cost-effectiveness by between 20 and 45 percent.[17]

Although the optimal strategy for delivering smoking cessation advice and intervention in the lung cancer screening setting has not yet been determined, prior research suggests that integrating smoking cessation into lung cancer screening programs takes advantage of a "teachable moment" for smoking behavior change, offering a potentially powerful motivation for action. The importance of cues to action is a now accepted precursor of behavior change. An individual's interpretation and judgment of an event determines whether it will prompt subsequent behavior change. McBride et al. suggest a teachable moment heuristic that includes three key constructs that underlie whether a cueing event is significant enough to be a teachable moment for smoking cessation: the extent to which the event (1) increases perceptions of personal risk and outcome expectancies, (2) prompts strong affective or emotional responses, and (3) redefines self-concept or social role.[59]
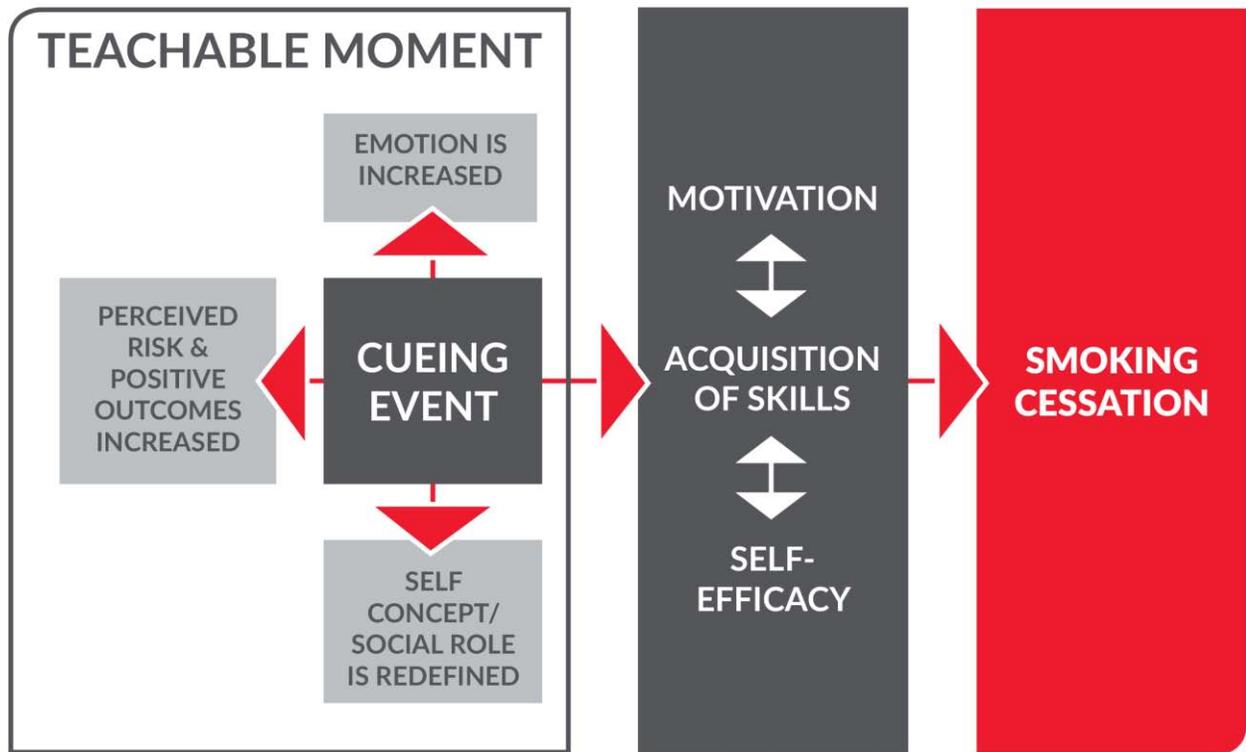
Screening provides an opportunity to personalize the health risks of persistent smoking, potentially drawing on the CT findings, including the presence of emphysema, and future risk of lung cancer. To date, tobacco-related biomedical risk markers (spirometry, exhaled carbon monoxide), have been used to communicate about the documentation of tobacco-related damage and exposure in order to motivate smokers to quit. The findings of LDCT offer additional markers to motivate cessation including evidence of coronary artery disease and COPD; the presence of such can be used to raise awareness of the risks of persistent smoking and the benefits of cessation for individuals who have been screened.

Cooley et al., reported that after diagnosis of cancer, around 50 percent of patients were interested in smoking cessation programs, further highlighting the need to develop such interventions in a way that optimizes effectiveness in the screening setting.[60] While studies vary regarding the degree to which participating in a lung cancer screening program affects smoking cessation, all guides recommend that lung cancer screening programs must promote smoking cessation, and that smoking cessation-related interventions are essential in any lung cancer screening program.[61]

As reported in publications on the NELSON,[62] I-ELCAP[63,64] and Mayo longitudinal studies,[65] participation in LDCT screening programs has been associated with quit rates that are two to three times those in the general population. In addition to reaching current smokers, screening offers an opportunity to counsel for relapse prevention among former smokers, both recent and long-term quitters. Lung cancer screening provides multiple opportunities for annual discussions about smoking cessation including during the initial screening discussion, at the screening appointment, and during initial and follow-up discussions. For participants in a lung cancer screening program, a screen result that is suspicious for lung cancer may provide further motivation to quit smoking. In one Mayo Clinic study, a dose-response relationship between false positive findings and improved quit rates was observed. Patients receiving one positive, two positive or three positive screening results had a 19.8 percent, 28 percent, and 41.9 percent quit rates, respectively. A similar dose-response relationship for the impact of positive findings on smoking status was observed in the NLST.[16]

Consistent with the US Public Health Service Clinical Practice Guidelines for Treating Tobacco Abuse and Dependence, the brief tobacco treatment model emphasizes five key steps (the five "As"):

1. **A**sk each patient about tobacco use
2. **A**dvise patient to quit
3. **A**ssess quit readiness
4. **A**ssist with quitting
5. **A**rrange follow-up

The existence of a covered preventive service for lung cancer screening becomes a "built in" or enhanced opportunity[i] for the health care provider to address smoking cessation.[66] During the discussion of the pros and cons of LDCT screening, current smokers who meet criteria for screening should receive a consistent and firm message with regard to the necessity of quitting. In addition, those who proceed with screening should receive a consistent message from the screening center personnel regarding the importance of smoking cessation. At each venue, the opportunities and modalities for smoking cessation should be introduced and offered in a consistent, easily accessible manner.

Using standardized metrics for smoking cessation outcomes can drive quality of care improvement and offering reimbursement for cessation will further incentivize providers to address smoking by screenees. It is also important to include standardized measures for assessing smoking cessation readiness and delivering quitting advice and assistance. Metrics similar in format to the National Quality Forum's of the Joint Commission for hospitals may be helpful in assessing the screening center's efficacy.[67] These should include:

1) Frequency of tobacco use screening
   - the number of individuals screened for tobacco use (numerator)
   - the number of individuals who present to a LDCT screening site (denominator)
2) Frequency of tobacco use treatment provided or offered at the time of LDCT screening
   - The number of individuals who received and refused practical counseling to quit (numerators) and
   - The number of individuals who received and refused FDA-approved cessation medications (numerators)
   - The number of individuals identified as current tobacco users (denominator)
3) Tobacco use assessment annually at each lung cancer screening appointment
4) Reassessment of smoking cessation at the time of annual repeat LDCT screening
5) Reassessment of smoking status at the time of re-evaluation of positive study

The aforementioned five As may also be used as a basis for guiding interactions with screening participants around smoking. We have also listed in Appendix I, a suggested protocol for health care providers to follow during interactions with high-risk patients being screened for lung cancer.

Additionally, the 2009 USPSTF recommendation on counseling and interventions to prevent tobacco use and tobacco-caused disease in adults[68] listed that the following strategies be included in practice to ensure successful implementation of smoking cessation advice:

- Instituting a tobacco user identification system.
- Promoting clinician intervention through education, resources and feedback.
- Dedicating staff to provide treatment, and assessing the delivery of treatment in staff performance evaluations.

Having standardized measures for smoking cessation advice and intervention included in a screening program can drive quality of care improvement. Offering reimbursement of these efforts will further incentivize providers. In addition to current smokers, relapse prevention among recent quitters and people who have received recent results should be covered. There is an opportunity to positively impact smoking cessation rates in the high-risk population.

The American Lung Association has a series of robust resources available nationwide, providing information and resources about quitting available at: http://www.lung.org/stop-smoking/how-to-quit/.

VII. Impact on COPD Diagnosis

A related consideration with LDCT involves the unprecedented potential to evaluate the status of other tobacco-related diseases through the imaging of the lung structure and the heart. The 2014 Report of the Surgeon General reports 480,000 annual deaths caused by tobacco use in the US.[23,69] Tobacco-exposed populations participating in lung cancer screening are known to experience a significant co-morbid risk of COPD and cardiovascular disease. COPD is defined as an expiratory airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles (tobacco smoke) or gases.[70] COPD includes patients with emphysema (the enlargement and destruction of the alveoli) and/or chronic bronchitis (chronic inflammation and scarring of the bronchial wall). The clinical diagnosis of COPD is generally made by means of spirometry, a safe and practical procedure when offered by a trained operator. The relative simplicity and low cost of spirometry allows potentially wide application of testing to improve recognition and diagnosis of COPD. COPD is a major public health concern with a prevalence of 6.4 percent in the US.[71] Men currently have lower COPD prevalence than women (5.4 vs 7.3 percent) and its occurrence increases among successive age groups and counties with higher poverty rates.[71] COPD remains substantially under-diagnosed in the community with an estimated total prevalence of 13.5 percent,[23] reflecting in large part the underuse of spirometry.[72]

The relationship between presence of COPD and risk for lung cancer has been well described. A recently published meta-analysis examined 39 studies on this association and concluded that COPD is associated with an increase in risk of lung cancer.[73] The summary relative risk for lung cancer associated with a diagnosis of COPD, either chronic bronchitis or emphysema, compared with people without this diagnosis was 1.83 [95% CI 1.6-2.11]. A more recent large case-control study carried out in the UK confirms smoking as a major risk factor for both COPD and lung cancer. In this study, after adjusting for smoking and time since COPD diagnosis, the risk of developing lung cancer was 2.18 times higher in smokers with COPD than those who are not susceptible to develop COPD.[74] There are two key implications of this evidence. First, because COPD is empirically a risk predictor for lung cancer, those with COPD are more likely to have lung cancer and should not be excluded from screening because COPD is present. Second, prediction models used to identify candidates for screening should incorporate the presence of COPD as it is an informative risk factor in smokers.

Recent reports have shown that the integration of LDCT assessment of lung damage as a metric of risk for COPD status is useful and can be implemented in the screening setting.[75] In a Dutch study, CT indicators of emphysema and air trapping were significantly associated with the presence of COPD, as documented by spirometry showing FEV_1/FVC ratio less than 70 percent. A predictive model was developed for the presence of COPD that incorporated the two CT-based indicators, body mass index and pack-years and smoking status. Among men who are current and former heavy smokers, using spirometry as the "gold standard", the model with the LDCT indicators identified participants with COPD with a sensitivity of 63 percent and a specificity of 88 percent

after the inclusion of expiratory scans. These results suggest that LDCT screening can contribute an integrated evaluation of COPD status and progression and that spirometric testing is necessary to confirm the diagnosis and assess the severity of the COPD. Furthermore, LDCT has been shown to be a useful tool for characterizing the extent of coronary calcium and stratification of risk of coronary artery disease.[76]

Emphysema status, as assessed with LDCT, has been shown to be a risk factor for mortality from COPD and lung cancer among asymptomatic smokers.[77] This finding is especially relevant when assessing the value of LDCT for complementing lung function testing. The LDCT information may help in selecting individuals who may benefit the most from smoking cessation in terms of reducing risk for COPD. Visual emphysema quantification based on LDCT plays also an important role in assessing the individual risk for lung cancer. The available results based on targeted studies suggest that the presence of emphysema on LDCT is an independent risk factor for lung cancer.[77–80] The identification of emphysema may therefore help in selecting people who may benefit the most from early detection and more advanced workup and CT findings related to emphysema should be considered in individual risk models that may guide the proper course of action. Findings from ongoing research that assesses the relationship between emphysema and lung cancer based on histological subtype and localization may lead to models with greater predictive accuracy.

LDCT COPD screening in the asymptomatic population for early detection of disease offers a new window of opportunity for the development of much needed therapeutic targets that has been elusive given the variability of spirometic measurements as endpoints. Under the stewardship of the COPD Foundation, the COPD biomarker qualification consortium is working toward reliable metrics, including quantitative CT markers, for drug development in COPD.[81] LDCT screening can provide the ideal framework to provide objective measurements of disease state and progression to assess new treatments in a population that can greatly benefit from early intervention options. The collateral benefits to the overall healthcare system could surpass the associated costs of screening in a population that is also at high risk for lung cancer.

LDCT screening offers the technical opportunity to simultaneously evaluate three major adverse consequences of tobacco smoking--cardiovascular disease, COPD and lung cancer--in an integrated fashion. However, while such evaluation is now technically possible, more work is needed related to implementation of this type of integrated analysis, which would call for follow-up of multiple diseases. Nevertheless, the current setting in which LDCT screening is being implemented can provide a useful window into the preclinical phases of three major chronic diseases.[82]

VIII. Updates on Imaging Quality and Exposure
Current technological advances in CT technology and reconstruction algorithms are allowing lower dose exposure with enhanced visual quality that may increase the feasibility of a joint protocol for COPD, CVD and lung cancer screening within the LDCT screening set up.[83] Iterative reconstruction methods can provide an equivalent image quality to current LDCT protocols while achieving a 60 percent reduction in dose (from 3.9 mGy to 1.6 mGy).[84] These new reconstruction techniques

introduce changes in the textural information from low contrast objects that may require a proper training of readers unfamiliar with this modality. Additional studies are needed to evaluate the consequences of using these techniques on visual and quantitative assessment within the clinical and screening set ups.

VIX. Conclusions

In March 2012, the American Lung Association Lung Cancer Screening Subcommittee released an interim report, shortly after publication of the findings of the NLST, with the following recommendations:

1. The best way to prevent lung cancer caused by tobacco use is to never start or quit smoking.
2. Low-dose CT screening should be recommended for those people who meet NLST criteria:
   o current or former smokers, aged 55 to 74 years
   o a smoking history of at least 30 pack-years
   o no history of lung cancer
3. Individuals should not receive a chest X-ray for lung cancer screening.
4. Low-dose CT screening should NOT be recommended for everyone.
5. 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:
   o the difference between a screening process and a diagnostic test
   o the benefits, risks and costs (emotional, physical and economic)
   o that not all lung cancers will be detected through use of low dose CT scanning
6. A call to action should be issued to hospitals and screening centers to:
   o establish ethical policies for advertising and promoting lung cancer CT screening services
   o develop educational materials to assist patients in having careful and thoughtful discussions between patients and their physicians regarding lung cancer screening
   o provide lung cancer screening services with access to multidisciplinary teams that can deliver the needed follow-up for evaluation of nodules.

As we have previously mentioned, the US Preventive Services Task Force (USPSTF) has issued its evaluation of the evidence, grading it at as "B" and recommending: "The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years." CMS announced its final coverage determination on February 5, 2015, covering the age range of 55-77 years, but important inconsistencies between the USPSTF population and the CMS recommendations for those eligible for screening remain.

- The Lung Association strongly believes that the proposed decision to provide LDCT screening to eligible Medicare beneficiaries is a crucial first step in reducing lung cancer deaths in those at the highest risk. As the screening process is further implemented in the real world setting, the Lung Association continues to urge Medicare to revise its eligibility criteria to be analogous with

those of the USPSTF final recommendations to alleviate confusion among providers and their patients as well as to ensure those most at need for screening receive the services.

- Implement the National Cancer Institute's National Lung Screening Trial's (NLST) recommendation that once a patient has qualified into a screening program, they are not forced to exit when they reach the 15-year mark of cessation.
- Refine the asymptomatic criteria to ensure that patients with chronic cough are not inappropriately excluded for screening and that those suspected of lung cancer a priori are sent through a diagnostic process rather than through the screening process.
- Allow for evidence development for those at-risk groups, e.g. high-risk workers, not included in the NLST, but for which biological plausibility exists for an increased risk of lung cancer.
- Consider the use of risk prediction models that incorporate not only age and smoking history, but also health status and the potential risks of diagnostic work-up and treatment in future coverage determinations. The NLST criteria represent a starting point but they do not capture all high-risk groups nor consider predicted risks.

Additionally, a number of professional organizations have released statements providing recommendations around lung cancer screening, including the American College of Radiology, the American College of Chest Physicians, the American Society of Clinical Oncology and the American Thoracic Society. The American Cancer Society and the International Association for the Study of Lung Cancer (IASLC) have also released recommendations. These recommendations have recommended screening and covered various technical, clinical and system issue related to screening.

This committee has reviewed these various recommendations and is in agreement with the major, common themes: 1) providing screening for persons meeting the profile of participants in the NLST; 2) carrying out screening in institutions that are able to provide a comprehensive screening program extending from the screening itself through all elements of follow-up work-up and care; and 3) implementing data systems that will assure program quality, track outcomes and support research. We emphasize the need for comprehensive data collection and analysis to generate the evidence needed to refine screening guidelines based on the "real world" experience that will document effectiveness. The NLST will not be repeated and, while trials are underway in Europe, their sample sizes are relatively small and their findings are unlikely to influence LDCT screening in the US. Thus, documentation of how well LDCT screening works in practice will be essential for guiding the evolution of lung cancer screening.

Based on its review of the evidence related to CT lung cancer screening, giving emphasis to more recent literature and experience amassed over the decade since the accrual to the NLST was completed, the Subcommittee offers the following guidance, directed particularly at the millions of people who turn to the American Lung Association for information and guidance on matters related to lung health:

- The Subcommittee reaffirms that the evidence from the NLST supports the implementation of lung cancer screening via LDCT. Experience to date also validates the Subcommittee's prior recommendations around institutional approaches to lung cancer screening, including the need for the availability of multidisciplinary clinical teams.
- Assessment of smoking and the provision of smoking cessation services must be part of any lung cancer screening program. Research is urgently needed to develop approaches that will maximize cessation rates among smokers undergoing screening.
- Present criteria for selecting candidates for LDCT largely follow the entry criteria of the NLST, e.g., those from the USPSTF and from CMS. The Subcommittee agrees that these criteria should be the starting point, but recommends that research should be carried out to support the development of risk-based criteria. While acknowledging that these criteria have implications for insurance coverage, the key clinical determinants of the appropriateness of screening include the underlying risk for lung cancer based on smoking history and age, as well as on health status and the potential risks of diagnostic work-up and treatment. The arbitrary age and smoking history criteria may not fit well with all clinical situations, e.g., a 50 year-old smoker with a 60-pack-year smoking history, and consequently the subcommittee urges that patients and their physicians carefully review risks and benefits with attention to the specifics of each person making a decision about screening. Accessible and patient-friendly risk prediction tools are needed to support decision-making. Data gathered on those receiving screening will be extremely useful for developing predictive models that will cover common clinical scenarios.
- Systematic data collection is requisite, and should cover detection of COPD and evidence of coronary artery disease. One model system has already been developed for that purpose—LungRADS.
- Gaps in evidence remain with regard to use of LDCT for lung cancer screening, extending across the full screening process. We recommend that a strategic research agenda be developed by a multi-stakeholder group to address the gaps; this is an opportunity for the ALA to assume leadership.
- CT screening for lung cancer may also identify previously undiagnosed COPD, given the smoking histories of those eligible for screening. Follow-up lung function testing should be incorporated into protocols, and carried out before any invasive work-up approaches are carried out.
- The ALA should develop a "Shared Decision-Making" toolkit(s) that would act as a "consumers' guide" for those considering lung cancer screening. The toolkit(s) should cover the following and be evaluated over time:
  o First time screening subject
    ▪ Guidance on selecting a particular institution as the venue for CT screening
    ▪ Indicators of program comprehensiveness and quality
    ▪ Eligibility criteria associated with coverage
    ▪ Results of scan and next steps
      • What is a pulmonary nodule?
      • What if they find a pulmonary nodule on my CT scan?

- What if they find evidence of COPD?
- What questions should I ask?
  - Screening candidates that are current smokers –
    - Providing information on how smoking cessation would enhance health outcomes beyond lung cancer
    - Emphasize resources to aid with smoking cessation
- Returning screening subject for annual repeat screen
  - Reviewing new developments over previous year
  - Eligibility criteria associated with coverage

Appendix I: Suggested cessation Protocol l for Health Care Providers

- Visit 1, referral to screening: Health Care Provider (HCP) discusses why the participant or is in the high-risk group including tobacco use, makes a strong recommendation to quit, assesses patient's readiness to quit, then conducts a more intensive discussion and referral to cessation services if the participant is ready to quit or provides referral materials if patient is not ready to quit. HCP will evaluate participant for medical appropriateness and willingness to use varenicline (Chantix) or bupropion (Zyban), as well as nicotine replacement therapy. HCP will provide prescriptions as appropriate.

- Visit 2, screening: If there is no clinician present at the screening, then tobacco cessation information and referral materials should be prominently available for distribution during the visit. Additionally, as a standard part of the screening protocol, the technician or clinician should ask about smoking status and readiness to quit.

- Visit 3, sharing screening results: HCP and participant discuss test results, HCP makes another strong recommendation to quit, assesses readiness to quit and (within the context of the test results) conducts a more intensive discussion and referral to services if patient is ready to quit or at least provides educational materials if patient is not ready yet to quit. Cessation medications are again recommended or discussed as appropriate. A follow-up appointment is scheduled if medications are prescribed.

References

1. American Cancer Society. *Cancer Facts & Figures 2014*.; 2014.
2. U.S. National Institutes of Health, Institute NC. *SEER Cancer Statistics Review, 1973–2011*.
3. Aberle DR, Adams AM, Berg CD, et al. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. *N Engl J Med*. 2011;365(5):395-409. doi:10.1056/NEJMoa1102873.
4. Veronesi G, Maisonneuve P, Bellomi M, et al. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. *Ann Intern Med*. 2012;157(11):776-784. doi:10.7326/0003-4819-157-11-201212040-00005.
5. Patz EF, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med*. 2014;174(2):269-274. doi:10.1001/jamainternmed.2013.12738.
6. *National Comprehensive Cancer Network, Clinical Practice Guidelines, Lung Cancer Screening, Version 2.2015*.
7. Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. *Cancer*. 2014;120(21):3401-3409. doi:10.1002/cncr.28833.
8. Van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *Br J Cancer*. 2010;102(1):27-34. doi:10.1038/sj.bjc.6605459.
9. Wiener RS, Gould MK, Woloshin S, Schwartz LM, Clark JA. "The thing is not knowing": patients' perspectives on surveillance of an indeterminate pulmonary nodule. *Health Expect*. 2012. doi:10.1111/hex.12036.
10. Slatore CG, Press N, Au DH, Curtis JR, Wiener RS, Ganzini L. What the heck is a "nodule"? A qualitative study of veterans with pulmonary nodules. *Ann Am Thorac Soc*. 2013;10(4):330-335. doi:10.1513/AnnalsATS.201304-080OC.
11. Jaklitsch MT, Jacobson FL, Austin JHM, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg*. 2012;144(1):33-38. doi:10.1016/j.jtcvs.2012.05.060.
12. National Comprehensive Cancer Centers. *Lung Screening Guideline*.; 2014.
13. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013;368(8):728-736. doi:10.1056/NEJMoa1211776.
14. Kovalchik SA, Tammemägi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med*. 2013;369(3):245-254. doi:10.1056/NEJMoa1301851.
15. McWilliams A, Tammemägi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med*. 2013;369(10):910-919. doi:10.1056/NEJMoa1214726.
16. Tammemägi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. *J Natl Cancer Inst*. 2014;106(6):dju084. doi:10.1093/jnci/dju084.
17. Villanti AC, Jiang Y, Abrams DB, Pyenson BS. A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. *PLoS One*. 2013;8(8):e71379. doi:10.1371/journal.pone.0071379.
18. Cressman S, Lam S, Tammemägi MC, et al. Resource Utilization and Costs during the Initial Years of Lung Cancer Screening with Computed Tomography in Canada. *J Thorac Oncol*. 2014;9(10):1449-1458. doi:10.1097/JTO.0000000000000283.
19. Black WC, Gareen IF, Soneji SS, et al. Cost-Effectiveness of CT Screening in the National Lung Screening Trial. *N Engl J Med*. 2014;371(19):1793-1802. doi:10.1056/NEJMoa1312547.

20.   Eberth JM, Qiu R, Adams SA, et al. Lung cancer screening using low-dose CT: the current national landscape. *Lung Cancer*. 2014;85(3):379-384. doi:10.1016/j.lungcan.2014.07.002.

21.   US Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA; 2004.

22.   Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Community Health*. 1978;32(4):303-313.

23.   US Department of Health and Human Services. *The Health Consequences of Smoking - 50 Years of Progress: A Report of the Surgeon General.* Atlanta, GA; 2014.

24.   International Agency for Research on Cancer. *Tobacco Smoke and Involuntary Smoking*. Lyon, France; 2004.

25.   Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879-1886.

26.   Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst*. 2003;95(6):470-478.

27.   Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. *J Natl Cancer Inst*. 2007;99(9):715-726. doi:10.1093/jnci/djk153.

28.   Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. *Br J Cancer*. 2008;98(2):270-276. doi:10.1038/sj.bjc.6604158.

29.   D'Amelio AM, Cassidy A, Asomaning K, et al. Comparison of discriminatory power and accuracy of three lung cancer risk models. *Br J Cancer*. 2010;103(3):423-429. doi:10.1038/sj.bjc.6605759.

30.   Etzel CJ, Bach PB. Estimating individual risk for lung cancer. *Semin Respir Crit Care Med*. 2011;32(1):3-9. doi:10.1055/s-0031-1272864.

31.   Spitz MR, Etzel CJ, Dong Q, et al. An expanded risk prediction model for lung cancer. *Cancer Prev Res (Phila)*. 2008;1(4):250-254. doi:10.1158/1940-6207.CAPR-08-0060.

32.   Spitz MR, Amos CI, Land S, et al. Role of selected genetic variants in lung cancer risk in African Americans. *J Thorac Oncol*. 2013;8(4):391-397. doi:10.1097/JTO.0b013e318283da29.

33.   Tammemägi MC, Lam SC, McWilliams AM, Sin DD. Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction. *Cancer Prev Res (Phila)*. 2011;4(4):552-561. doi:10.1158/1940-6207.CAPR-10-0183.

34.   Raji OY, Duffy SW, Agbaje OF, et al. Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. *Ann Intern Med*. 2012;157(4):242-250. doi:10.7326/0003-4819-157-4-201208210-00004.

35.   Li H, Yang L, Zhao X, et al. Prediction of lung cancer risk in a Chinese population using a multifactorial genetic model. *BMC Med Genet*. 2012;13:118. doi:10.1186/1471-2350-13-118.

36.   Park S, Nam B-H, Yang H-R, et al. Individualized risk prediction model for lung cancer in Korean men. *PLoS One*. 2013;8(2):e54823. doi:10.1371/journal.pone.0054823.

37.   Etzel CJ, Kachroo S, Liu M, et al. Development and validation of a lung cancer risk prediction model for African-Americans. *Cancer Prev Res (Phila)*. 2008;1(4):255-265. doi:10.1158/1940-6207.CAPR-08-0082.

38.   Wang X, Oldani MJ, Zhao X, Huang X, Qian D. A review of cancer risk prediction models with genetic variants. *Cancer Inform*. 2014;13(Suppl 2):19-28. doi:10.4137/CIN.S13788.

39.   Raji OY, Agbaje OF, Duffy SW, Cassidy A, Field JK. Incorporation of a genetic factor into an epidemiologic model for prediction of individual risk of lung cancer: the Liverpool Lung Project. *Cancer Prev Res (Phila)*. 2010;3(5):664-669. doi:10.1158/1940-6207.CAPR-09-0141.

40. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med*. 2013;369(10):920-931. doi:10.1056/NEJMoa1208962.

41. Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. *Lung Cancer*. 2001;32(3):227-236.

42. Wisnivesky JP, Mushlin AI, Sicherman N, Henschke C. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. *Chest*. 2003;124(2):614-621.

43. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA*. 2003;289(3):313-322.

44. Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. *Lung Cancer*. 2005;48(2):171-185. doi:10.1016/j.lungcan.2004.11.001.

45. McMahon PM, Kong CY, Bouzan C, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. *J Thorac Oncol*. 2011;6(11):1841-1848. doi:10.1097/JTO.0b013e31822e59b3.

46. Pyenson BS, Henschke CI, Yankelevitz DF, Yip R, Dec E. Offering lung cancer screening to high-risk medicare beneficiaries saves lives and is cost-effective: an actuarial analysis. *Am Heal drug benefits*. 2014;7(5):272-282.

47. Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An Actuarial Analysis Shows That Offering Lung Cancer Screening As An Insurance Benefit Would Save Lives At Relatively Low Cost. *Health Aff*. 2012;31(4):770-779. doi:10.1377/hlthaff.2011.0814.

48. Flores R, Bauer T, Aye R, et al. Balancing curability and unnecessary surgery in the context of computed tomography screening for lung cancer. *J Thorac Cardiovasc Surg*. 2014;147(5):1619-1626. doi:10.1016/j.jtcvs.2013.11.001.

49. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Ann Intern Med*. 2011;155(3):137-144. doi:10.1059/0003-4819-155-3-201108020-00003.

50. Miller KS, Fish GB, Stanley JH, Schabel SI. Prediction of pneumothorax rate in percutaneous needle aspiration of the lung. *Chest*. 1988;93(4):742-745.

51. Boffa DJ, Allen MS, Grab JD, Gaissert HA, Harpole DH, Wright CD. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. *J Thorac Cardiovasc Surg*. 2008;135(2):247-254. doi:10.1016/j.jtcvs.2007.07.060.

52. Cheung MC, Hamilton K, Sherman R, et al. Impact of teaching facility status and high-volume centers on outcomes for lung cancer resection: an examination of 13,469 surgical patients. *Ann Surg Oncol*. 2009;16(1):3-13. doi:10.1245/s10434-008-0025-9.

53. Little AG, Rusch VW, Bonner JA, et al. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg*. 2005;80(6):2051-2056; discussion 2056. doi:10.1016/j.athoracsur.2005.06.071.

54. Meguid RA, Brooke BS, Chang DC, Sherwood JT, Brock M V, Yang SC. Are surgical outcomes for lung cancer resections improved at teaching hospitals? *Ann Thorac Surg*. 2008;85(3):1015-1024; discussion 1024-1025. doi:10.1016/j.athoracsur.2007.09.046.

55. Flores RM, Park BJ, Dycoco J, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. *J Thorac Cardiovasc Surg*. 2009;138(1):11-18. doi:10.1016/j.jtcvs.2009.03.030.

56. Scott WJ, Allen MS, Darling G, et al. Video-assisted thoracic surgery versus open lobectomy for lung cancer: a secondary analysis of data from the American College of Surgeons Oncology Group Z0030

randomized clinical trial. *J Thorac Cardiovasc Surg*. 2010;139(4):976-981; discussion 981-983. doi:10.1016/j.jtcvs.2009.11.059.

57. Hattotuwa K, Gamble EA, O'Shaughnessy T, Jeffery PK, Barnes NC. Safety of bronchoscopy, biopsy, and BAL in research patients with COPD. *Chest*. 2002;122(6):1909-1912.

58. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e166S - 90S. doi:10.1378/chest.12-2395.

59. McBride C, Emmons K, Lipkus I. Understanding the potential of teachable moments: the case of smoking cessation. *Health Educ Res*. 2003;18(2):156-170.

60. Cooley ME, Emmons KM, Haddad R, et al. Patient-reported receipt of and interest in smoking-cessation interventions after a diagnosis of cancer. *Cancer*. 2011;117(13):2961-2969. doi:10.1002/cncr.25828.

61. Munshi V, McMahon P. Importance of Smoking Cessation in a Lung Cancer Screening Program. *Curr Surg reports*. 2013;1(4). doi:10.1007/s40137-013-0030-1.

62. Van der Aalst CM, van Klaveren RJ, van den Bergh KAM, Willemsen MC, de Koning HJ. The impact of a lung cancer computed tomography screening result on smoking abstinence. *Eur Respir J*. 2011;37(6):1466-1473. doi:10.1183/09031936.00035410.

63. Anderson CM, Yip R, Henschke CI, Yankelevitz DF, Ostroff JS, Burns DM. Smoking cessation and relapse during a lung cancer screening program. *Cancer Epidemiol Biomarkers Prev*. 2009;18(12):3476-3483. doi:10.1158/1055-9965.EPI-09-0176.

64. Ostroff JS, Buckshee N, Mancuso CA, Yankelevitz DF, Henschke CI. Smoking cessation following CT screening for early detection of lung cancer. *Prev Med (Baltim)*. 2001;33(6):613-621. doi:10.1006/pmed.2001.0935.

65. Townsend CO, Clark MM, Jett JR, et al. Relation between smoking cessation and receiving results from three annual spiral chest computed tomography scans for lung carcinoma screening. *Cancer*. 2005;103(10):2154-2162. doi:10.1002/cncr.21045.

66. Panel TU and DG. Specific Populations and Other Topics.

67. National Quality Forum. Behavorial Health Endorsement Summaries.

68. U.S. Preventive Services Task Force (USPSTF). Final Recommendation Statement: Tobacco Use in Adults and Pregnant Women: Counseling and Interventions. 2009.

69. Rostron BL, Chang CM, Pechacek TF. Estimation of cigarette smoking-attributable morbidity in the United States. *JAMA Intern Med*. 2014;174(12):1922-1928. doi:10.1001/jamainternmed.2014.5219.

70. Rennard SI. COPD: overview of definitions, epidemiology, and factors influencing its development. *Chest*. 1998;113(4 Suppl):235S - 241S.

71. Zhang X, Holt JB, Lu H, et al. Multilevel regression and poststratification for small-area estimation of population health outcomes: a case study of chronic obstructive pulmonary disease prevalence using the behavioral risk factor surveillance system. *Am J Epidemiol*. 2014;179(8):1025-1033. doi:10.1093/aje/kwu018.

72. Johns DP, Walters JAE, Walters EH. Diagnosis and early detection of COPD using spirometry. *J Thorac Dis*. 2014;6(11):1557-1569. doi:10.3978/j.issn.2072-1439.2014.08.18.

73. Brenner DR, McLaughlin JR, Hung RJ. Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. *PLoS One*. 2011;6(3):e17479. doi:10.1371/journal.pone.0017479.

74. Powell HA, Iyen-Omofoman B, Baldwin DR, Hubbard RB, Tata LJ. Chronic obstructive pulmonary disease and risk of lung cancer: the importance of smoking and timing of diagnosis. *J Thorac Oncol*. 2013;8(1):6-11. doi:10.1097/JTO.0b013e318274a7dc.

75. Mets OM, Buckens CFM, Zanen P, et al. Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. *JAMA*. 2011;306(16):1775-1781. doi:10.1001/jama.2011.1531.

76. Shemesh J, Henschke CI, Shaham D, et al. Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease. *Radiology*. 2010;257(2):541-548. doi:10.1148/radiol.10100383.

77. Zulueta JJ, Wisnivesky JP, Henschke CI, et al. Emphysema Scores Predict Death from Chronic Obstructive Pulmonary Disease and Lung Cancer. *Chest*. 2011. doi:10.1378/chest.11-0101.

78. De Torres JP, Bastarrika G, Wisnivesky JP, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest*. 2007;132(6):1932-1938. doi:10.1378/chest.07-1490.

79. Gierada DS, Guniganti P, Newman BJ, et al. Quantitative CT assessment of emphysema and airways in relation to lung cancer risk. *Radiology*. 2011;261(3):950-959. doi:10.1148/radiol.11110542.

80. Smith BM, Pinto L, Ezer N, Sverzellati N, Muro S, Schwartzman K. Emphysema detected on computed tomography and risk of lung cancer: a systematic review and meta-analysis. *Lung Cancer*. 2012;77(1):58-63. doi:10.1016/j.lungcan.2012.02.019.

81. Casaburi R, Celli B, Crapo J, et al. The COPD Biomarker Qualification Consortium (CBQC). *COPD*. 2013;10(3):367-377. doi:10.3109/15412555.2012.752807.

82. Mulshine JL, D'Amico TA. Issues with implementing a high-quality lung cancer screening program. *CA Cancer J Clin*. 64(5):352-363. doi:10.3322/caac.21239.

83. Kulkarni NM, Pinho DF, Kambadakone AR, Sahani D V. Emerging technologies in CT- radiation dose reduction and dual-energy CT. *Semin Roentgenol*. 2013;48(3):192-202. doi:10.1053/j.ro.2013.03.007.

84. Mathieu KB, Ai H, Fox PS, et al. Radiation dose reduction for CT lung cancer screening using ASIR and MBIR: a phantom study. *J Appl Clin Med Phys*. 2014;15(2):4515.