LUNG CANCER ALLIANCE

SAVING LIVES AND ADVANCING RESEARCH BY EMPOWERING THOSE LIVING WITH AND AT RISK FOR LUNG CANCER.

LungCancerAlliance.org

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The Society of Thoracic Surgeons

ACR® AMERICAN COLLEGE OF RADIOLOGY

May 30, 2018

USPSTF
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality
5600 Fishers Lane
Mailstop 06E53A
Rockville, Maryland 20857

*Electronic Submission:* Online Comments

**Re: USPSTF Draft Research Plan for Lung Cancer Screening**

Dear USPSTF Members:

Lung Cancer Alliance (LCA), American College of Radiology (ACR), and The Society of Thoracic Surgeons (STS), are national societies representing lung cancer patients, survivors and caregivers, and diagnostic radiologists, radiation oncologists, nuclear medicine physicians, medical physicists, and thoracic surgeons, appreciate the opportunity to comment as a coalition on the USPSTF Draft Research Plan for Lung Cancer Screening. We applaud the efforts to address this public health issue and implement recommendations on a preventive service that will help address the leading cause of cancer death; nearly a third of this nation's total cancer mortality burden. We collectively support the following comments in response to the specific USPSTF draft research plan questions, as well as provide additional independent responses to the draft research plan by our respective organizations.

Our joint societies support the importance of establishing the right preventive service for lung cancer screening and respectfully recommend the draft research plan questions:

- Remove bias from the analytic framework (overwhelming emphasis on harms and no mention of benefit)
- Add "low dose" (for accuracy, low dose should be specified throughout the framework for every question regarding CT)

- Include Post Market Surveillance data as well as other well-designed research approaches (reliance only on RCTs has limitations for lung cancer screening)
- Include questions and data analysis on the overall harms to the population when you do not screen the at-risk population including additional groups such as “NCCN 2” category

Lung cancer is the leading cause of cancer for both men and women. More than 156,000 patients die from lung cancer each year in the United States, a figure that is greater than the mortality rates of breast, prostate, and colon cancer combined. Furthermore, lung cancer is the leading cause of cancer death in every racial and ethnic subgroup, and is the leading cancer killer of women, taking more lives than breast and every gynecological cancer combined.

Lung cancer screening (LCS) with low dose CT (LDCT) is the only procedure proven to reduce lung cancer mortality in individuals at high-risk for lung cancer. There is a high level of evidence that screening is cost-effective and can lead to early diagnosis and cure. A responsible and ethical expanded screening recommendation is needed for at-risk populations.

**Harms and Benefits**

From an overarching observation, the USPSTF analytic framework projects a bias towards harms with greater usage of, and reference to, the term "harms" and no reference to "benefit." The framework should be revised to show objectivity and not predisposition or unintended bias towards harms that could undermine public faith and confidence in the objectiveness of the review. The uptake of screening is complex and comes with moral responsibility in implementing a preventive service based on the cancer death rate and public health need. To be unduly pessimistic with low dose CT lung cancer screening without real-world data and allowance of time for realistic uptake may be harmful.

It is important to understand and convey in the framework and to the public that the structure of the National Lung Screening Trial (NLST) and its corresponding data, while significant, is not the sole basis for optimal screening. This particular randomized control trial was started 16 years ago, focused on detecting a threshold level of screening mortality reduction benefit and not structured for public health or screening implementation. The USPSTF should address the benefits to the public, so they understand that low dose CT screening over the course of the at-risk public’s broader screening eligibility likely has additional benefit beyond the narrow NLST trial parameters.

We recommend that the USPSTF's efforts to define the harms/benefit for lung cancer screening consider how misrepresentation of harms may compromise the realization of potential lung cancer screening benefit. It is a harm to the public when false positivity rates of screening are overstated, and outdated risks are being conveyed to patients as "the truth" when there are new data and protocols that have drastically decreased false positives.

Since the NLST reporting, management protocols and technology have significantly improved and advanced with higher specificity and sensitivity with standardized approaches. Low dose CT technology has advanced and is now far more refined, in addition to standardized reporting and management tools. For example, Lung-RADS, Nelson, and I-ELCAP define a positive test as a two-step process resulting in a more accurate level of sensitivity and specificity. Also, measures to define the accuracy of screening must specify whether they relate to Baseline (prevalence) or annual follow up (incidence) rounds of screening as these contexts are different. The context is important, as the rate of cancer detection should be the same for each annual screening round but different from the detection rate at baseline.

There have been many approaches reported since the NLST that improve the efficiency of LDCT detection of early lung cancer which should be recognized and evaluated by the USPSTF. For example, ACR Lung-RADS addresses false positives and reduces this rate by 75% compared to prior studies. The NELSON Dutch/Belgian screening trial published in NEJM concludes accuracy of screening with 95% sensitivity and 98% specificity and compared to breast and colon cancers, the lung cancer screening accuracy is remarkable. In addition, while the NLST reported a 26% false positive rate, with a two-step cancer detection process, this rate was reduced to 12.8% (Lung-RADS) and reduced even further to 5.3% (Lung-RADS) after baseline, 3% (I-ELCAP), and 2.1% (UKLS). This process can continue to improve continued research of this implemented service.

Within the context of the NLST, the issue of benefit versus harm for surgical management of early-stage lung cancer has already been answered with the demonstration of significant decrease in lung cancer and all-cause mortality. Outside the NLST, there are well-established data documenting the results of surgical management of early-stage lung cancer including both institutional reports and registry analyses. Any objective assessment of surgical efficacy should use contemporary results reported within the last decade such as data from screening studies (e.g., I-ELCAP). One must be wary of the results from international centers which would include patients with widely varying clinical status, heterogeneous staging practices, and unknown levels of clinical expertise. In addition to surgical management of early-stage lung cancer, other therapeutic modalities have advanced and should be included in the USPSTF analysis (i.e., SBRT, standard RT and chemotherapy, immunotherapy).

**RCTs and Post Market Surveillance Data**

While efforts are underway to inform providers and the public through training and education, we caution against heightened expectations and demands for data within a short ramp-up interval as this could be detrimental to public health. We are just over 3-years from the February 2015 National Coverage Determination (NCD) on lung cancer screening and still earlier for private provider reimbursement for this service, as there were many delays and setbacks with HCPCS and ICD9-10 coding and claims recognition. Given the state of capabilities to capture lung cancer screening results, it is extremely optimistic or premature to be looking for all-cause mortality outcomes at this early juncture.

Instead, we recommend that post-market evaluation is utilized in conjunction with RCTs (e.g., NLST). Post-marketing surveillance considers real-world experiences to inform the clinical conversation and strategy. The FDA understood the benefits of a pragmatic file design and, for example, has implemented a process to assess benefit and impact of particular vaccination programs. To help refine best practices through dialogue and clinical practice, we refer you to programs like the LCA *National Framework for Excellence in Lung Cancer Screening in the Continuum of Care*, a peer-peer network currently consisting of over 550 hospitals located in 42 states and DC, across settings that have committed to following best practice principles of care. This dynamic and evolving network is a national pilot program capturing data and proving lung cancer screening is scalable and replicable in a standardized way within the community setting. The network shares lessons learned in real- time and adjusts and adapts their services to reduce barriers, improve access and accelerate uptakes in screening. Data compiled from ACR Designated Lung Cancer Screening Centers may also be helpful in this endeavor. The question for the USPSTF in this review must be focused on the implementation experience associated with the cancer detection approach.

The USPSTF questions should also look at the harms associated with the need for additional education among the ordering physicians and the patient. Twelve thousand people per year may die due to lack of screening according to the ASCO study, and based on extremely low screening rates, the majority of eligible patients never hear there is a test they may benefit from. There remains provider ignorance of and non-compliance with lung cancer screening guidelines, provider prejudice and bias against former and current smokers, and perpetuation of health care disparities in populations disproportionately affected by lung cancer (elderly, minorities, lower socioeconomic status). Those who believe money spent on screening should be redirected to smoking cessation completely discount the benefit of screening for nearly-40 million former smokers who remain at elevated risk for lung cancer. The abundant medical literature points to a pervasive lack of patient and physician education on the benefits of screening, and the low Medicare reimbursement for LDCT, especially in the hospital outpatient setting, increase challenges with uptake and may be harmful.

The complexity of the implemented lung cancer screening shared decision making (SDM) process may also be exerting an unintentional barrier to participation. The SDM requirement is uniquely applied to lung cancer screening and should have the equivalent evidence-based standards through studies to show the harms and benefits. As it currently stands, SDM is cumbersome, administratively and financially burdensome, and focused inappropriately on harms versus benefits.

**Additional At-risk Population**

In a recent NEJM publication, a study confirmed higher lung cancer rates in white and Hispanic women in comparison to men. Also, lung cancer physicians are seeing more and more female patients who have never smoked. The study concluded that when people stop smoking their risk of developing cancer drops every year. However, the risk for a common type of cancer, adenocarcinoma, drops more slowly than that for other types of lung cancer. Adenocarcinoma develops more frequently in women than men. The lead epidemiologist in the study, Ahmedin Jemal, stated: "one hypothesis that the reduction in the risk of lung cancer after smoking cessation may be slower in women than in men."

It is critical to review real-world evidence to address the unique impact on disparate populations including the underserved and minorities, as well as women. Women who may have stopped smoking more than 15 years ago, may be at higher risk than men. The baseline for getting screened should be re-evaluated on the overall need and benefits beyond the asymptomatic smokers, and former smokers between the ages of 55 and 80 who have at least 30 pack-years of smoking and have used tobacco within the last 15 years.

Although these individuals were not studied by the NLST, the risk of smoking-related cancers is predominantly related to total exposure and gradually decreases over time, meaning that these patients may remain at significant risk of lung cancer development. Further, an arbitrary cutoff of 15 years would result in an implementation dilemma for patients who are covered for initiation of lung cancer screening, and who are then no longer covered for continued follow-up and screening after they have succeeded in smoking cessation for more than 15 years. This exclusion could potentially lead to a paradox of incentives that “encourages” a patient to restart smoking in order to maintain eligibility for lung cancer screening coverage.

We believe there is clear and promising evidence [e.g., International Early Lung Cancer Action Program (I-ELCAP) framework, protocol, and workup recommendations; Lahey studies for other patient populations, NCCN guidelines] to show the screening benefits in individuals who have >30 pack-years of smoking history but have stopped smoking for more than 15 years. In fact, multiple risk calculators for lung cancer all utilize additional factors beyond age and smoking history that were used for inclusion criteria in the NLST. Additional lung cancer risk factors should be considered in assuring equitable access to lung cancer screening in patients at similar risks of lung cancer to

those studied in the NLST, but for which no randomized trial, is currently, nor likely will be independently reported.

**Summary**

We urge the USPSTF to seek objective information that will provide an accurate evidence base for at-risk individuals considering lung cancer screening. In addition, we urge the USPSTF to incorporate the balance of risks with additional life years gained across all high-risk populations at risk for lung cancer, and not just those that are at the highest risk. The critical issue at this point is how to optimize lung cancer screening implementation efficiently, while simultaneously promoting the safe detection of and proper management of early-stage, potentially curable lung cancer.

The USPSTF is limited in such an analysis as no comprehensive source of relevant outcomes data exists for our nation. To assist the USPSTF in its mission, we advocate for the establishment of a comprehensive national surveillance capability to help facilitate the responsible implementation of lung cancer screening. In the time since the completion of the NLST, we have already seen marked improvements in medical radiation exposure, overdiagnosis, false-positivity rate, surgical management as well as other aspects of lung cancer screening management. With a comprehensive surveillance capability, the evolution of lung cancer screening care can rapidly evolve to an even more favorable benefit-to-harms ratio for this critical service.

In summary, careful consideration of the analytic framework should be evaluated based on the balance of overall harms and benefits within the context of this public health issue taking 156,000 thousand lives every year in the United States. Our joint societies thank you for this opportunity to comment on this important life-saving preventive service.

Sincerely,

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William T. Thorwarth, Jr., MD, FACR
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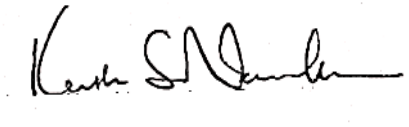

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