September 9, 2013

Louis B. Jacques, MD
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Blvd
Baltimore MD 21244

Formal Request for a National Coverage Determination on Lung Cancer Screening with Low Dose Computed Tomography

Dear Dr. Jacques,

I am writing to submit a formal Track # 1 request for a National Coverage Determination (NCD) on whether the use of Low Dose Computed Tomography (LDCT) is reasonable and necessary for the early detection of lung cancer (i.e. lung cancer screening) in beneficiaries at high risk of developing the disease. The probable Medicare Benefit Category for lung cancer screening with LDCT is Preventive and Screening Services described by section 1861(s)(2)(BB) of the Social Security Act. Coverage is allowable for Medicare if the United States Preventive Services Task Force (USPSTF) endorses LDCT screening with an "A" or "B" recommendation. The procedure currently has an "I" grade from the USPSTF, but an update is in progress and the Task Force released a draft recommendation on July 30th, 2013 with a "B" grade, roughly aligning the task force recommendations with those of many organizations.[1-6]

In line with the findings and recommendations of the medical literature related to this screening test I am requesting that the Centers for Medicare and Medicaid Services (CMS) determine that screening for lung cancer with LDCT when conducted in centers with appropriate expertise and staffing is reasonable and necessary for those beneficiaries who are between 55 and 74 years of age, are current smokers (or have quit smoking within the last 15 years) and have a smoking history of at least 30 pack years (defined as number of packs smoked per day multiplied by number of years smoked). It should be covered under Coverage with Evidence Development using a patient specific registry designed to ask several important unanswered questions about screening and its impact on beneficiaries that I detail in my request, and it should only be covered for beneficiaries who elect to receive the service after a data driven decision making discussion with their physician.

The following pages and attachments contain the necessary supporting documentation for this NCD request as specified by CMS in the Federal Register (Vol. 68, No. 187, page 55637). Thank you for taking the time to review and consider this request.

Sincerely,

Peter B. Bach
Director, Center for Health Policy and Outcomes
Department of Epidemiology and Biostatistics
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, NY

Supporting Documentation

I. A full and complete description of the item or service in question

Computed tomography (CT or CAT scan) is a radiologic imaging procedure which produces cross sectional pictures of the body, providing a detailed of view of organs, bones and other tissues. Low dose computed tomography (LDCT) is a version of a CT scan that aims to minimize the patient's exposure to radiation from the procedure. LDCT has been seen as a potential advance in lung cancer screening due to its advantages in accuracy and radiation minimization when compared to CXR and regular dose CT, respectively.[7] Computed tomography has been approved as a class II medical device by the United States Food and Drug Administration for diagnostic uses, but not for screening.

II. A specific detailed description of the proposed use of the item or service, including the target Medicare population and the medical condition(s) for which it can be used

The target population includes beneficiaries between the ages of 55 and 74, who are either current smokers or have quit smoking within the last fifteen years and have a smoking history of at least thirty pack years. Beneficiaries with any of the following characteristics should not be included in the target population: history of aerodigestive cancer; individuals undergoing active treatment for any cancer; history of removal of any portion of the lung, excluding small tissue biopsies via needle or bronchoscopic biopsy; requirement for home oxygen supplementation; unexplained weight loss of more than 15 pounds in the 12 months prior; recent hemoptysis; pneumonia or acute respiratory infection treated with antibiotics in the 12 weeks prior to eligibility assessment; chest CT examination in the 18 months prior; individuals with a life expectancy of less than 5 years.[7] Beneficiaries with a past history of lung cancer should not be eligible for the service as imaging of the chest in these individuals constitutes use of the CT scanner as a diagnostic service under a different benefit category that is already covered for Medicare beneficiaries when conducted appropriately.

Note that pack years are defined as the duration of smoking history (years) multiplied by the intensity of smoking history (packs smoked per day). Some example smoking histories that equate to 30 pack years include smoking one pack per day for 30 years and smoking 2 packs per day for 15 years.

III. An explanation of the design, purpose and method of using the item or equipment, including whether the item is for use by health care practitioners or patients

The service is for the use of qualified health practitioners to proactively search for lung cancer in patients who are asymptomatic but at high risk of developing the disease (screening). It is not intended to screen for or diagnose other diseases or disorders although related incidental findings are occasionally uncovered.

IV. A description of any clinical trials currently underway that might be relevant to a decision regarding coverage of the item or service

There are several ongoing randomized trials, and several that are completed but for which some important analyses are pending, including a planned cost-effectiveness analysis of data derived from the NLST trial. The USPSTF is also currently in the process of updating their recommendations on the topic (for updated information see: http://www.uspreventiveservicestaskforce.org/uspstf/topicsprog.htm). This review will determine if

the service earns an A or a B recommendation which would provide statutory authority for CMS to include this screening service in the benefit for Medicare enrollees (the currently available "draft" recommendations have issued a "B" grade). The ongoing studies are described in detail within the table located at the end of this document.

V. A compilation of the supporting medical and scientific information currently available that measures the medical benefits of the item or service

A list of the peer-reviewed publications relevant to the medical benefits of screening for lung cancer with LDCT is located at the end of this document. These publications are described below in section VI and a full text version of each of the articles is included in an attachment.

VI. Statement from the requestor regarding the evidence for lung cancer screening with LDCT

A. An Explanation of the relevance of the evidence selected

With this request I am submitting a comprehensive set of published studies on lung cancer CT screening derived from a recent systematic review published in the Journal of the American Medical Association, as well as relevant studies published since that review was published. The key inclusions are the review itself regarding the benefits and harms of lung cancer screening using LDCT,[2] the three randomized controlled trials (RCTs) comparing the benefit of screening with LDCT to that of screening with chest x-ray (CXR),[7-12] six RCTs comparing the benefit of screening with LDCT to that of no screening,[13-22] one RCT comparing the benefit of screening with CXR to no screening,[23] thirteen observational cohort studies which evaluate LDCT screening[24-43] and five sets of clinical practice guidelines on the use of LDCT for lung cancer screening.[1-4,6] The studies not included in the review include a more recently published RCT,[13] the USPSTF's draft updated recommendation statement, evidence report and modeling report,[5,44,45] a risk prediction model based on NLST data[46] and an editorial discussing the variation in benefit likely to be seen across eligible patients who differ in their baseline risk of developing lung cancer.[47] Note that several of the RCTs and cohort studies have multiple publications. All of the selected RCTs and cohort studies are limited to individuals at high risk of developing lung cancer due to age and significant smoking histories among other factors, although the eligibility criteria due differ along with other aspects of the intervention.

B. Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population

Cancer screening tests necessarily involve tradeoffs. Numerous individuals who will never suffer from the condition being screened for are subjected to the test and many have findings on the test that lead to follow-up evaluations which carry risks and costs. Yet a few individuals who undergo effective screening tests benefit due to the early detection of a condition that can have its outcome altered through early intervention. The systematic review of the evidence regarding the benefits and harms of LDCT screening outlines these respective potential harms and benefits and forms the basis for many of the current practice guidelines for lung cancer screening. The guidelines are listed below in the table. The review, and all of the clinical practice guidelines concluded that LDCT screening for lung cancer may benefit a specific target population of Medicare beneficiaries (current smokers, or former smokers who have quit within the last 15 years, are between the ages of 55-74 and have a smoking history of at least 30 py) and recommended that the test be offered to those patients by their clinicians. Two sets of guidelines (from NCCN and AATS), as well as the draft update to the USPSTF's recommendation

September 9, 2013

Louis B. Jacques, MD
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Blvd
Baltimore MD 21244

Formal Request for a National Coverage Determination on Lung Cancer Screening with Low Dose Computed Tomography

Dear Dr. Jacques,

I am writing to submit a formal Track # 1 request for a National Coverage Determination (NCD) on whether the use of Low Dose Computed Tomography (LDCT) is reasonable and necessary for the early detection of lung cancer (i.e. lung cancer screening) in beneficiaries at high risk of developing the disease. The probable Medicare Benefit Category for lung cancer screening with LDCT is Preventive and Screening Services described by section 1861(s)(2)(BB) of the Social Security Act. Coverage is allowable for Medicare if the United States Preventive Services Task Force (USPSTF) endorses LDCT screening with an "A" or "B" recommendation. The procedure currently has an "I" grade from the USPSTF, but an update is in progress and the Task Force released a draft recommendation on July 30th, 2013 with a "B" grade, roughly aligning the task force recommendations with those of many organizations.[1-6]

In line with the findings and recommendations of the medical literature related to this screening test I am requesting that the Centers for Medicare and Medicaid Services (CMS) determine that screening for lung cancer with LDCT when conducted in centers with appropriate expertise and staffing is reasonable and necessary for those beneficiaries who are between 55 and 74 years of age, are current smokers (or have quit smoking within the last 15 years) and have a smoking history of at least 30 pack years (defined as number of packs smoked per day multiplied by number of years smoked). It should be covered under Coverage with Evidence Development using a patient specific registry designed to ask several important unanswered questions about screening and its impact on beneficiaries that I detail in my request, and it should only be covered for beneficiaries who elect to receive the service after a data driven decision making discussion with their physician.

The following pages and attachments contain the necessary supporting documentation for this NCD request as specified by CMS in the Federal Register (Vol. 68, No. 187, page 55637). Thank you for taking the time to review and consider this request.

Sincerely,

Peter B. Bach
Director, Center for Health Policy and Outcomes
Department of Epidemiology and Biostatistics
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, NY

Supporting Documentation

I. A full and complete description of the item or service in question

Computed tomography (CT or CAT scan) is a radiologic imaging procedure which produces cross sectional pictures of the body, providing a detailed of view of organs, bones and other tissues. Low dose computed tomography (LDCT) is a version of a CT scan that aims to minimize the patient's exposure to radiation from the procedure. LDCT has been seen as a potential advance in lung cancer screening due to its advantages in accuracy and radiation minimization when compared to CXR and regular dose CT, respectively.[7] Computed tomography has been approved as a class II medical device by the United States Food and Drug Administration for diagnostic uses, but not for screening.

II. A specific detailed description of the proposed use of the item or service, including the target Medicare population and the medical condition(s) for which it can be used

The target population includes beneficiaries between the ages of 55 and 74, who are either current smokers or have quit smoking within the last fifteen years and have a smoking history of at least thirty pack years. Beneficiaries with any of the following characteristics should not be included in the target population: history of aerodigestive cancer; individuals undergoing active treatment for any cancer; history of removal of any portion of the lung, excluding small tissue biopsies via needle or bronchoscopic biopsy; requirement for home oxygen supplementation; unexplained weight loss of more than 15 pounds in the 12 months prior; recent hemoptysis; pneumonia or acute respiratory infection treated with antibiotics in the 12 weeks prior to eligibility assessment; chest CT examination in the 18 months prior; individuals with a life expectancy of less than 5 years.[7] Beneficiaries with a past history of lung cancer should not be eligible for the service as imaging of the chest in these individuals constitutes use of the CT scanner as a diagnostic service under a different benefit category that is already covered for Medicare beneficiaries when conducted appropriately.

Note that pack years are defined as the duration of smoking history (years) multiplied by the intensity of smoking history (packs smoked per day). Some example smoking histories that equate to 30 pack years include smoking one pack per day for 30 years and smoking 2 packs per day for 15 years.

III. An explanation of the design, purpose and method of using the item or equipment, including whether the item is for use by health care practitioners or patients

The service is for the use of qualified health practitioners to proactively search for lung cancer in patients who are asymptomatic but at high risk of developing the disease (screening). It is not intended to screen for or diagnose other diseases or disorders although related incidental findings are occasionally uncovered.

IV. A description of any clinical trials currently underway that might be relevant to a decision regarding coverage of the item or service

There are several ongoing randomized trials, and several that are completed but for which some important analyses are pending, including a planned cost-effectiveness analysis of data derived from the NLST trial. The USPSTF is also currently in the process of updating their recommendations on the topic (for updated information see: http://www.uspreventiveservicestaskforce.org/uspstf/topicsprog.htm). This review will determine if

the service earns an A or a B recommendation which would provide statutory authority for CMS to include this screening service in the benefit for Medicare enrollees (the currently available "draft" recommendations have issued a "B" grade). The ongoing studies are described in detail within the table located at the end of this document.

V. A compilation of the supporting medical and scientific information currently available that measures the medical benefits of the item or service

A list of the peer-reviewed publications relevant to the medical benefits of screening for lung cancer with LDCT is located at the end of this document. These publications are described below in section VI and a full text version of each of the articles is included in an attachment.

VI. Statement from the requestor regarding the evidence for lung cancer screening with LDCT

A. An Explanation of the relevance of the evidence selected

With this request I am submitting a comprehensive set of published studies on lung cancer CT screening derived from a recent systematic review published in the Journal of the American Medical Association, as well as relevant studies published since that review was published. The key inclusions are the review itself regarding the benefits and harms of lung cancer screening using LDCT,[2] the three randomized controlled trials (RCTs) comparing the benefit of screening with LDCT to that of screening with chest x-ray (CXR),[7-12] six RCTs comparing the benefit of screening with LDCT to that of no screening,[13-22] one RCT comparing the benefit of screening with CXR to no screening,[23] thirteen observational cohort studies which evaluate LDCT screening[24-43] and five sets of clinical practice guidelines on the use of LDCT for lung cancer screening.[1-4,6] The studies not included in the review include a more recently published RCT,[13] the USPSTF's draft updated recommendation statement, evidence report and modeling report,[5,44,45] a risk prediction model based on NLST data[46] and an editorial discussing the variation in benefit likely to be seen across eligible patients who differ in their baseline risk of developing lung cancer.[47] Note that several of the RCTs and cohort studies have multiple publications. All of the selected RCTs and cohort studies are limited to individuals at high risk of developing lung cancer due to age and significant smoking histories among other factors, although the eligibility criteria due differ along with other aspects of the intervention.

B. Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population

Cancer screening tests necessarily involve tradeoffs. Numerous individuals who will never suffer from the condition being screened for are subjected to the test and many have findings on the test that lead to follow-up evaluations which carry risks and costs. Yet a few individuals who undergo effective screening tests benefit due to the early detection of a condition that can have its outcome altered through early intervention. The systematic review of the evidence regarding the benefits and harms of LDCT screening outlines these respective potential harms and benefits and forms the basis for many of the current practice guidelines for lung cancer screening. The guidelines are listed below in the table. The review, and all of the clinical practice guidelines concluded that LDCT screening for lung cancer may benefit a specific target population of Medicare beneficiaries (current smokers, or former smokers who have quit within the last 15 years, are between the ages of 55-74 and have a smoking history of at least 30 py) and recommended that the test be offered to those patients by their clinicians. Two sets of guidelines (from NCCN and AATS), as well as the draft update to the USPSTF's recommendation

statement, also proposed screening some other individuals whose risk of lung cancer was (in the guideline writers judgment) sufficiently high.[3-5]

All the guidelines share a cautious tone regarding the harms of screening and the expertise that is necessary to perform screening in the least harmful and most beneficial way possible. The guidelines from ASCO, ACCP and ATS note the importance of screening individuals only in settings that are able to deliver comprehensive care similar to that received by NLST participants.[2] These screening recommendations came with several other caveats including the following: counseling should include a complete description of potential benefits and harms so the individual can decided whether to undergo LDCT screening; screening should be conducted in a center similar to those where the NLST was conducted, with multidisciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers. The USPSTF's draft recommendation statement and the AATS guidelines also acknowledge that limiting screening to settings with capabilities similar to those of the NLST sites could be beneficial.[5]

The guidelines released by ASCO, ACCP and the ATS also recommended what is generally agreed upon within the evidence based community concerned with lung cancer screening, which is that a registry is needed to determine if LDCT screening conducted in individuals not in the clinical studies yields the same findings and measures of harm that were seen in the NLST study. Concerns about external validity of the NLST results stem from unanswered questions about the technical, structural and clinical components of LDCT screening. On the technical = and structural sides there are the demographic makeup of NLST participants compared to the NLST-eligible population nationwide, the previously mentioned issues related to the atypical nature of the NLST sites and the associated individual radiologists and other health professionals, as well as issues related to the equipment used, such as collimation settings and scan quality of the CT scanners.

The NLST was conducted in # sites throughout the US. 76% of these sites were NCI designated comprehensive cancer centers.[2] The significance of this designation is evident in the fact that it is received by only 41 of the 5,000+ hospitals in the country. Further, 82% of NLST sites were large academic medical centers with more than 400 beds. The population screened in the NLST was also different, in important ways, from the NLST-eligible population nationwide. In comparison to the population of individuals in the US who meet the NLST eligibility criteria for age and smoking history, the NLST study subjects were more highly educated (31.5% vs 14.4% with a college degree or higher), younger (73% vs 65% under 65 years of age) and less likely to be current smokers (48% vs 57%). These characteristics suggest that the NLST population was healthier than the typical NLST-eligible individual, which would bias the NLST results towards greater benefits and fewer harms.[9]

Clinically, reported rates of false positives of LDCT screening have been extremely variable, varying by study from less than 5% to nearly 50%.[2] Similarly, reported rates of followup surgical procedures varied from less than 1% to nearly 6%.[2] The 60 day mortality rate following lung resection in the NLST was only 1 percent (meaning 30 day and in-hospital mortality were lower than this figure).[8] Meanwhile, an analysis of the Nationwide Inpatient Sample suggests that in 2010 the average in-hospital mortality rate following lobectomy was 1.9%.[48] Important questions about the effects of LDCT screening on smoking behavior also remain unanswered. Differences in the prevalence and intensity of smoking, as well as rates of cessation and recidivism, between the population eligible for screening under Medicare and the NLST population could limit the effectiveness of screening. These sources of uncertainty surrounding the external validity of the NLST results could be addressed through the use of a well designed patient registry including, among other items, data on nodule detection and

statement, also proposed screening some other individuals whose risk of lung cancer was (in the guideline writers judgment) sufficiently high.[3-5]

All the guidelines share a cautious tone regarding the harms of screening and the expertise that is necessary to perform screening in the least harmful and most beneficial way possible. The guidelines from ASCO, ACCP and ATS note the importance of screening individuals only in settings that are able to deliver comprehensive care similar to that received by NLST participants.[2] These screening recommendations came with several other caveats including the following: counseling should include a complete description of potential benefits and harms so the individual can decided whether to undergo LDCT screening; screening should be conducted in a center similar to those where the NLST was conducted, with multidisciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers. The USPSTF's draft recommendation statement and the AATS guidelines also acknowledge that limiting screening to settings with capabilities similar to those of the NLST sites could be beneficial.[5]

The guidelines released by ASCO, ACCP and the ATS also recommended what is generally agreed upon within the evidence based community concerned with lung cancer screening, which is that a registry is needed to determine if LDCT screening conducted in individuals not in the clinical studies yields the same findings and measures of harm that were seen in the NLST study. Concerns about external validity of the NLST results stem from unanswered questions about the technical, structural and clinical components of LDCT screening. On the technical = and structural sides there are the demographic makeup of NLST participants compared to the NLST-eligible population nationwide, the previously mentioned issues related to the atypical nature of the NLST sites and the associated individual radiologists and other health professionals, as well as issues related to the equipment used, such as collimation settings and scan quality of the CT scanners.

The NLST was conducted in # sites throughout the US. 76% of these sites were NCI designated comprehensive cancer centers.[2] The significance of this designation is evident in the fact that it is received by only 41 of the 5,000+ hospitals in the country. Further, 82% of NLST sites were large academic medical centers with more than 400 beds. The population screened in the NLST was also different, in important ways, from the NLST-eligible population nationwide. In comparison to the population of individuals in the US who meet the NLST eligibility criteria for age and smoking history, the NLST study subjects were more highly educated (31.5% vs 14.4% with a college degree or higher), younger (73% vs 65% under 65 years of age) and less likely to be current smokers (48% vs 57%). These characteristics suggest that the NLST population was healthier than the typical NLST-eligible individual, which would bias the NLST results towards greater benefits and fewer harms.[9]

Clinically, reported rates of false positives of LDCT screening have been extremely variable, varying by study from less than 5% to nearly 50%.[2] Similarly, reported rates of followup surgical procedures varied from less than 1% to nearly 6%.[2] The 60 day mortality rate following lung resection in the NLST was only 1 percent (meaning 30 day and in-hospital mortality were lower than this figure).[8] Meanwhile, an analysis of the Nationwide Inpatient Sample suggests that in 2010 the average in-hospital mortality rate following lobectomy was 1.9%.[48] Important questions about the effects of LDCT screening on smoking behavior also remain unanswered. Differences in the prevalence and intensity of smoking, as well as rates of cessation and recidivism, between the population eligible for screening under Medicare and the NLST population could limit the effectiveness of screening. These sources of uncertainty surrounding the external validity of the NLST results could be addressed through the use of a well designed patient registry including, among other items, data on nodule detection and

characteristics, follow-up testing, radiation exposure, patient experience, and smoking behavior. Screening quality metrics that could be assessed through this registry should also be developed.

Three additional sets of clinical practice guidelines (or similar documents) released by the National Comprehensive Cancer Network, the American Association of Thoracic Surgeons and American Lung Association came to similar conclusions and made similar recommendations, although the former two societies recommended screening some additional populations.[1,3,4]

Table: Summary of Recommendations on Lung Cancer Screening Completed by US-based Professional Societies and Government Agencies

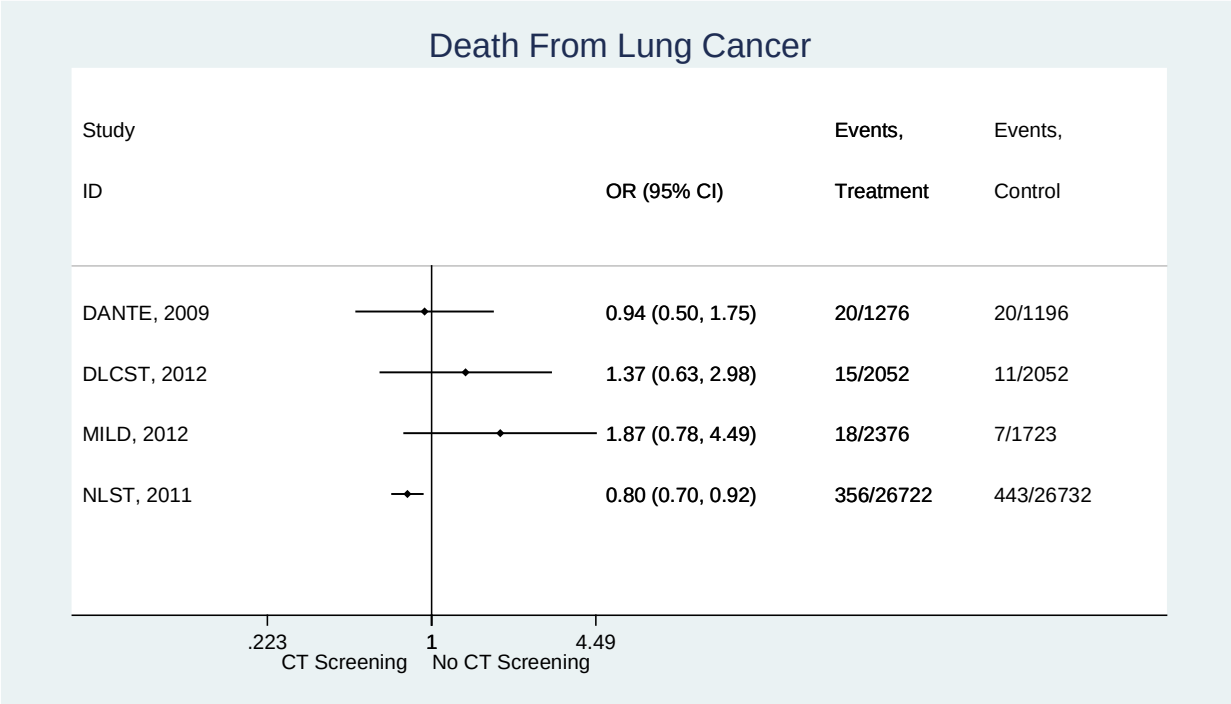
<table>
<tr><td>Recommend screening NLST eligible groups[1]</td><td colspan="2">AATS, ACCP, ACS, ALA, ASCO, ATS, NCCN, USPSTF(draft)[2]</td></tr>
<tr><td rowspan="3">Also recommend screening other groups</td><td>AATS</td><td>Screen up to age 79. Screening may begin at age 50 with 20 pack years if 5 year risk of lung cancer is >5%.</td></tr>
<tr><td>NCCN</td><td>Screening may begin at age 50 with 20 pack years if one additional risk factor is present.[3]</td></tr>
<tr><td>USPSTF(draft)[1]</td><td>Screen up to age 79.</td></tr>
</table>

1: Individuals between 55 and 74 years of age, who are current smokers (or have quit smoking within the last 15 years) and have a smoking history of at least 30 pack years (defined as number of packs smoked per day multiplied by number of years smoked).
2: The USPSTF is currently in the process of completing their updated recommendation on lung cancer screening. The recommendations referred to in this table are currently in 'draft' form. Information on the status of the USPSTF recommendation is available at: http://www.uspreventiveservicestaskforce.org/uspstf/topicsprog.htm
3: Relevant additional risk factors according to NCCN include cancer history, lung disease history, family history of lung cancer, radon exposure and occupational exposure to asbestos or another carcinogen.[4]

C. Information that examines the magnitude of the medical benefit

Four RCTs, the National Lung Screening Trial (NLST)[8], the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial (DANTE),[15] the Danish Lung Cancer Screening Trial (DLCST),[19] and the Multicentric Italian Lung Detection Study (MILD)[13] have reported results on the effect of LDCT screening for lung cancer on mortality. All four trials reported data on all cause and lung cancer specific mortality, as well as (indirectly or directly) mortality from all causes other than lung cancer. The NLST found that 3 annual rounds of screening with LDCT resulted in a 20% relative decrease in deaths from lung cancer vs CXR over a median of 6.5 years of follow-up (P=.004).[8] In absolute terms, the chance of dying from lung cancer was 0.33% less over the study period in the LDCT group. The smaller DANTE, DLCST and MILD studies each compared a planned 5 annual rounds of screening to usual care and, after 34, 58 and 53 months of followup, respectively, found no statistically significant difference in lung cancer mortality between screened and unscreened groups (figure).[15,19] No study found a significant difference in deaths not due to lung cancer resulting from screening either individually or combined.[8]

Figure generated by requestor:



It should be noted that the results presented in the above forest plot, taken from the systematic review by Bach et. al., differ slightly from those in the USPSTF's evidence report. Using reported person months of followup (instead of the median as in Bach et. al.) the USPSTF evidence report found RRs for lung cancer mortality of 0.83 (95% CI: 0.45 – 1.54) in the DANTE trial and 1.99 (95% CI: 0.8 – 4.96) in the MILD trial.[45]

A fifth RCT, the Prostate, Lung, Colorectal and Ovarian Randomized Trial (PLCO), found no mortality difference between CXR screening and usual care among individuals who would have been eligible for the NLST, allowing the control populations in the NLST, DANTE, MILD and DLCST trials to be considered reasonably comparable, even though the NLST used CXR screening rather than usual care as the control intervention.[23] It is important to note that although all of these studies restricted eligibility to individuals at high risk of lung cancer, the NLST, which was the only study to find a mortality benefit from LDCT screening, used the most restrictive eligibility criteria and appears as a result to have screened a population at higher risk of developing lung cancer than the DANTE, DLCST and MILD trials.

Potential harms of LDCT screening for lung cancer include false positive results, complications resulting from diagnostic procedures (following either true positive or false positive results), overdiagnosed cancers, exposure to radiation, and detriments to quality of life. As detailed by Bach et al most of the RCT and cohort studies evaluating LDCT screening report on the frequency of false positive results and unnecessary diagnostic procedures as well as the complications resulting from both necessary and unnecessary diagnostic procedures.[2] However, there is substantial heterogeneity in the manner in which these results are reported and in the results themselves. Across studies approximately 20% in each round of screening had a positive result requiring some degree of followup, while approximately 1% had lung cancer.[2] Regarding the risks of radiation exposure, models estimate that the radiation risks associated with LDCT screening are outweighed by the benefits for NLST eligible individuals, although this is not necessarily the case for individuals at lower risk of developing lung

cancer.[2] The evidence available on overdiagnosis (detection of cancers that would not affect the patient's life if left untreated) and quality of life issues related to LDCT screening for lung cancer is very limited and more evidence is needed to draw conclusions in these areas.[2]

As previously mentioned, LDCT screening could potentially have benefits (or harms) related to smoking behavior if there are differences in the prevalence and intensity of smoking, as well as rates of cessation and recidivism, between populations who receive LDCT screening and those who do not. The evidence on these outcomes in studies of LDCT screening is limited and mixed. According to the USPSTF's evidence report multiple trials found no difference in smoking behavior between treatment and control groups, although one of the two showed increased smoking abstinence among those with abnormal findings.[45] Results from cohort studies were also varied.[45]

There is substantial variation between patients in the benefits that can be expected from lung cancer screening based on their underlying risk factors. Within the NLST eligible population the estimated number of lung cancer deaths averted with LDCT screening varies fifteen fold, as shown in the table below.[47] At the same time, the variety of harms associated with LDCT screening described above, such as false positive screening results and their associated effects on quality of life, may affect individuals in different and personal ways.

Table. **Projected Likelihood Over 6 Years of Lung Cancer Death With or Without Screening per 1000 Persons Screened***

Participant	Risk Factors	Deaths From Lung Cancer (Without Screening) per 1000 Persons, *n*	Deaths From Lung Cancer (With Screening) per 1000 Persons, *n*	Lung Cancer Deaths Averted per 1000 Persons, *n*	Persons Needed to Be Screened Annually for 3 y to Prevent 1 Death From Lung Cancer Over 6 y, *n*
"Typical" participant in the NLST	62-year-old male current 1.5-PPD smoker for 35 y	19.5	15.6	3.9	256
Minimum eligible participant in the NLST	55-year-old female former 1-PPD smoker for 30 y who just quit	4.0	3.2	0.8	1236
High-risk participant eligible for the NLST	70-year-old current 2-PPD smoker for 55 y	60.9	48.7	12.2	82
Minimum eligible participant by NCCN guidelines	50-year-old male former 1-PPD smoker for 20 y who quit 10 y ago with an occupational asbestos exposure history	1.6	1.3	0.3	3180
Low-risk eligible participant for Sequoia Hospital lung screening program	40-year-old female former 1-PPD smoker for 10 y who quit 15 y ago	0.10	0.08	0.02	35 186

NCCN = National Comprehensive Cancer Network; NLST = National Lung Screening Trial; PPD = packs per day.
* Assuming the program includes 3 y of annual screening.

For these reasons lung cancer screening is an example of a health care decision in which there is a reasonable likelihood that a patient's preferences would affect the probability for an approach to be considered optimal. Therefore, screening for lung cancer is a clear example of a situation in which Informed or Shared Decision Making (SDM) should be applied. SDM is a collaborative process that allows patients and their providers to make health care decisions together, taking into account the best scientific evidence available, as well as the patient's values and preferences. The utilization of well established SDM methods should play a role in Medicare's coverage of LDCT screening for lung cancer. Several validated prediction models are available which could form the basis of tools that will facilitate a SDM process. These models have been shown to produce similar estimates and have been used in the development of multiple publicly available electronic risk prediction tools (images).[46,49-52]

Image: Screenshot of the MSKCC Lung Cancer Risk Prediction Tool

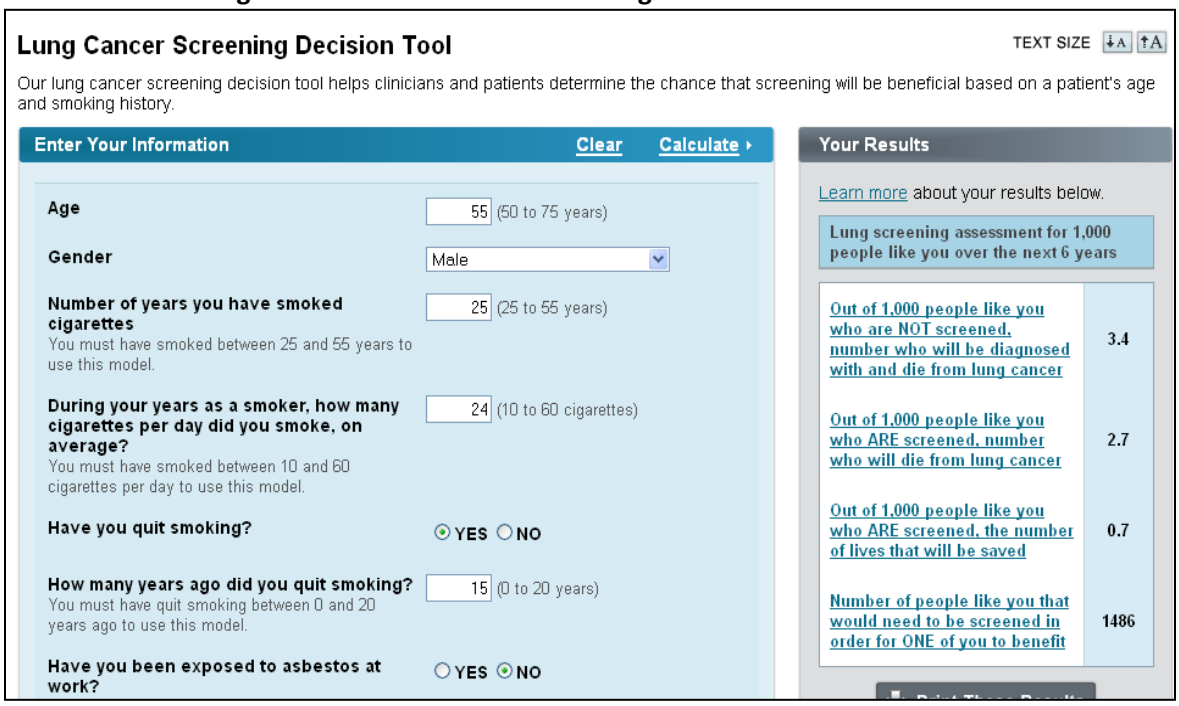
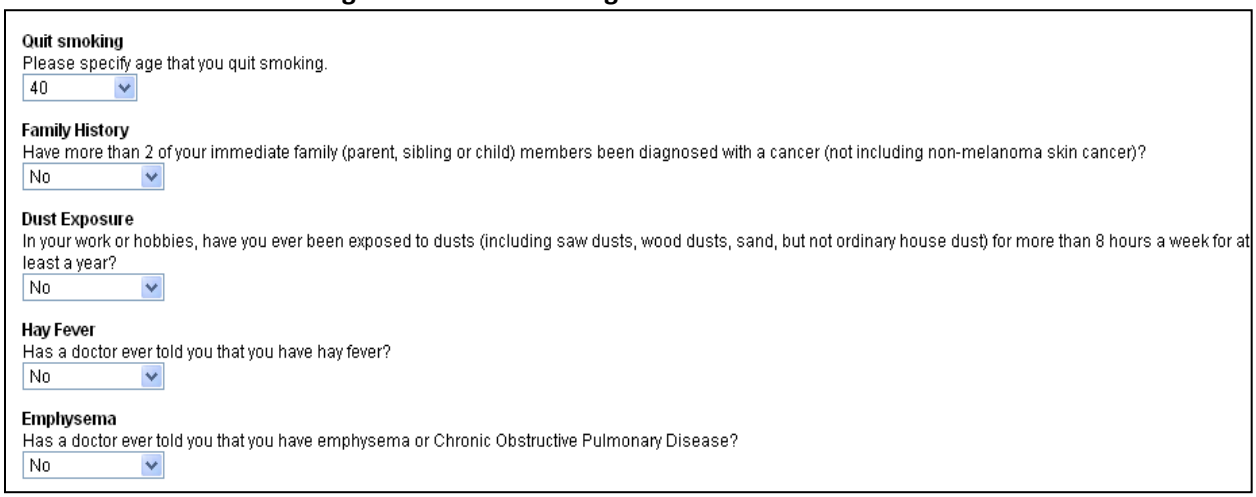
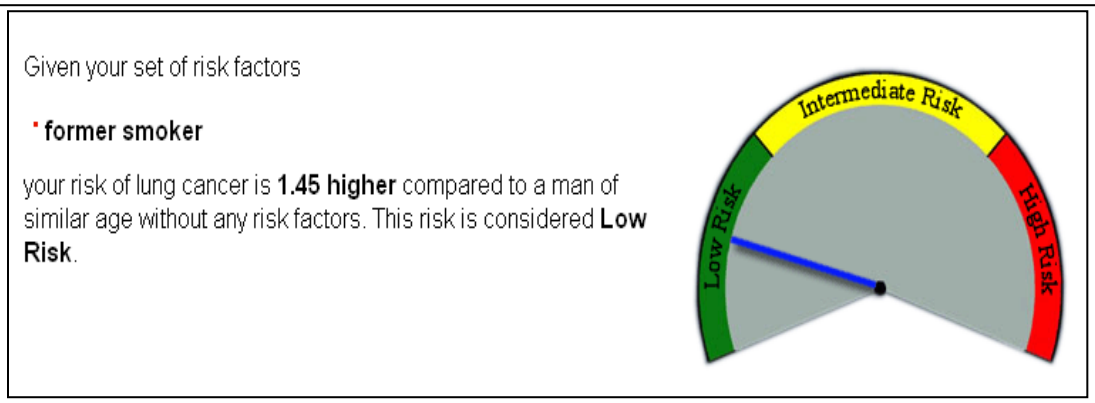


Image: MD Anderson Lung Cancer Risk Prediction Tool





D. Reasoning for how coverage of the item or service will help improve the medical benefit to the target population

Coverage of the screening test will improve the medical benefit by enabling access to a procedure that has been found to reduce lung cancer mortality in individuals at substantially elevated risk of lung cancer in the setting of a large federally funded study with a high degree of oversight conducted at large highly experienced centers. It is now recommended by seven separate medical professional organizations based in the United States and the USPSTF has issued a "B" grade in the form of draft recommendations. To maximize the benefit and minimize the harms of the procedure, coverage should be limited to centers of excellence that are able to provide the comprehensive level of care that was made available to NLST participants. Characteristics of these centers should be defined by the agency in collaboration with experts in the field. A screening registry should be mandated using coverage with evidence development process to ensure that benefits, harms, and processes are continually monitored when beneficiaries are being screened and their findings are being further evaluated. The registry would be used to address unanswered questions regarding the external validity of the NLST mortality results, rates of false positives and related followup procedures, and the effects of LDCT screening on smoking behavior. The use of shared decision making is vitally important and LDCT screening should only be covered if the patient chooses to be screened after being informed of the benefits and harms of screening in a data driven discussion, through the use of SDM methods, with their physician.

List of publications (full text versions of each article are included in a separate attachment)

1. Providing Guidance on Lung Cancer Screening to Patients and Physicians. 2012. (Accessed 1/25/2013, at http://www.lung.org/lung-disease/lung-cancer/lung-cancer-screening-guidelines/lung-cancer-screening.pdf.)
2. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA : the journal of the American Medical Association 2012;307:2418-29.
3. Jaklitsch MT, Jacobson FL, Austin JH, 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. The Journal of thoracic and cardiovascular surgery 2012;144:33-8.
4. NCCN Clinical Practice Guidelines in Oncology: Lung Cancer Screening (Version 1.2014). (Accessed 8/14/2013, at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#lung_screening.)
5. Lung Cancer Screening Draft Recomendation Statement. AHRQ Publication No. 13-05196-EF-3. 2013. (Accessed 9/6/2013, at http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcandraftrec.htm.)
6. Wender R, Fontham ET, Barrera E, Jr., et al. American Cancer Society lung cancer screening guidelines. CA: a cancer journal for clinicians 2013.
7. Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. Radiology 2011;258:243-53.
8. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. The New England journal of medicine 2011;365:395-409.
9. Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized national lung screening trial. Journal of the National Cancer Institute 2010;102:1771-9.
10. Blanchon T, Brechot JM, Grenier PA, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). Lung Cancer 2007;58:50-8.
11. Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. Chest 2004;126:114-21.
12. Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer 2005;47:9-15.
13. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2012;21:308-15.
14. Garg K, Keith RL, Byers T, et al. Randomized controlled trial with low-dose spiral CT for lung cancer screening: feasibility study and preliminary results. Radiology 2002;225:506-10.
15. Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med 2009;180:445-53.
16. Infante M, Chiesa G, Solomon D, et al. Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2011;6:327-35.
17. Lopes Pegna A, Picozzi G, Mascalchi M, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer 2009;64:34-40.

18. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2009;4:608-14.
19. Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax 2012;67:296-301.
20. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. The New England journal of medicine 2009;361:2221-9.
21. Ashraf H, Tonnesen P, Holst Pedersen J, Dirksen A, Thorsen H, Dossing M. Effect of CT screening on smoking habits at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). Thorax 2009;64:388-92.
22. van der Aalst CM, van den Bergh KA, Willemsen MC, de Koning HJ, van Klaveren RJ. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. Thorax 2010;65:600-5.
23. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA : the journal of the American Medical Association 2011;306:1865-73.
24. Bastarrika G, Garcia-Velloso MJ, Lozano MD, et al. Early lung cancer detection using spiral computed tomography and positron emission tomography. Am J Respir Crit Care Med 2005;171:1378-83.
25. Callol L, Roig F, Cuevas A, et al. Low-dose CT: a useful and accessible tool for the early diagnosis of lung cancer in selected populations. Lung Cancer 2007;56:217-21.
26. Diederich S, Thomas M, Semik M, et al. Screening for early lung cancer with low-dose spiral computed tomography: results of annual follow-up examinations in asymptomatic smokers. Eur Radiol 2004;14:691-702.
27. Diederich S, Wormanns D, Lenzen H, Semik M, Thomas M, Peters PE. Screening for asymptomatic early bronchogenic carcinoma with low dose CT of the chest. Cancer 2000;89:2483-4.
28. Diederich S, Wormanns D, Semik M, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology 2002;222:773-81.
29. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early lung cancer action project: initial findings on repeat screenings. Cancer 2001;92:153-9.
30. Henschke CI, Yankelevitz DF, Libby DM, et al. Early lung cancer action project: annual screening using single-slice helical CT. Ann N Y Acad Sci 2001;952:124-34.
31. MacRedmond R, Logan PM, Lee M, Kenny D, Foley C, Costello RW. Screening for lung cancer using low dose CT scanning. Thorax 2004;59:237-41.
32. MacRedmond R, McVey G, Lee M, et al. Screening for lung cancer using low dose CT scanning: results of 2 year follow up. Thorax 2006;61:54-6.
33. Menezes RJ, Roberts HC, Paul NS, et al. Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience. Lung Cancer 2010;67:177-83.
34. Novello S, Fava C, Borasio P, et al. Three-year findings of an early lung cancer detection feasibility study with low-dose spiral computed tomography in heavy smokers. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2005;16:1662-6.
35. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003;362:593-7.
36. Picozzi G, Paci E, Lopez Pegna A, et al. Screening of lung cancer with low dose spiral CT: results of a three year pilot study and design of the randomised controlled trial ''Italung-CT''. Radiol Med 2005;109:17-26.

37. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002;20:911-20.
38. Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. Radiology 2005;235:259-65.
39. Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003;226:756-61.
40. Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002;165:508-13.
41. Veronesi G, Bellomi M, Mulshine JL, et al. Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. Lung Cancer 2008;61:340-9.
42. Veronesi G, Bellomi M, Scanagatta P, et al. Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program. The Journal of thoracic and cardiovascular surgery 2008;136:611-7.
43. Wilson DO, Weissfeld JL, Fuhrman CR, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med 2008;178:956-61.
44. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and Harms of Computed Tomography Lung Cancer Screening Programs for High-Risk Populations. 2013.
45. Humphrey LL, Deffebach M, Pappas M, et al. Screening for Lung Cancer With Low-Dose Computed Tomography: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Annals of internal medicine 2013.
46. Tammemagi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. The New England journal of medicine 2013;368:728-36.
47. Bach PB, Gould MK. When the average applies to no one: personalized decision making about potential benefits of lung cancer screening. Annals of internal medicine 2012;157:571-3.
48. Bach PB. Perilous Potential: The Chance to Save Lives, or Lose them, Through Low Dose Computed Tomography Screening for Lung Cancer Journal of Surgical Oncology 2013;In press.
49. Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. Journal of the National Cancer Institute 2003;95:470-8.
50. Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. British journal of cancer 2008;98:270-6.
51. Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. Journal of the National Cancer Institute 2007;99:715-26.
52. Tammemagi CM, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial models and validation. Journal of the National Cancer Institute 2011;103:1058-68.
53. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. Thorax 2011;66:308-13.
54. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. Journal of cancer research and clinical oncology 2012;138:1475-86.

Trials Currently in Progress for Lung Cancer Screening with LDCT

Study	Number of Participants			Screening with LDCT			Study Duration		Number of Screens			Participant Characteristics			
	Randomized (total)	% Screened or Followed at Baseline by Trial Arm		Collimation (mm)	Nodule Size (mm) Warranting Work-up (↑ Imaging, Diagnostic Tests)	Is a Diagnostic Protocol in Place?	Years of Accrual	Planned Years of Follow-up from Baseline	Planned	Completed (at last report)	Conducted Annually?	Male	Age Range	Smoking History Eligibility (current or former)	
		LDCT	Control											Pack-Years [a]	Years since quit
LDCT versus Usual Care (no screening)															
NELSON[20]	15,822 [b]	95%	100%	0.75	≥ 4.6 / > 9.8	Yes [c]	2004-NR	10	3	2	No [d]	84%	50-75	> 15	≤ 10
DLCST[18]	4,104	100%	100%	0.75 [e]	≥ 5 / > 15	Yes	2004-06	10	5	1	Yes	55%	50-70	> 20	< 10 [f]
ITALUNG[17]	3,206	87%	100%	1-1.25	≥ 5 / ≥ 8 [g]	Yes	-	-	4	1	Yes	65%	55-69	≥ 20	< 10
UKLS[53]	32,000 (planned)	TBA	TBA	0.5-0.625	≥ 15	Yes	TBA	10	1	0	NA	TBA	50-75	NA[i]	
LUSI[54]	4,052	TBA	TBA	NR	≥ 5	Yes	2007-2011	NR	5	4	Yes	TBA	50-69	≥ 15	< 10
LDCT versus Chest X-Ray															
NLST [j]	53,454	98%	97%	≤ 2.5	≥ 4	Yes	2002-04	> 7	3	3	Yes	59%	55-74	≥ 30	≤ 15

Note: NR = Not Reported, The column heading Nodule Size (mm) Warranting Work-up indicates first the largest size nodule warranting additional imaging, and second the largest size nodule warranting diagnostic testing

[a] Pack-years is defined as the number of cigarettes packs (20 cigarettes per pack) smoked per day multiplied by the number of years smoked.

[b] Randomization is ongoing with a target accrual of 16000 participants.

[c] A protocol was reported, however specific details on adherence or deviation from the protocol or actual procedures used were not reported.

[d] Planned screening at years 1,2, and 4.

[e] Collimation = 16 x 0.75 mm

[f] Former smokers had to have quit after the age of 50 years and less than 10 years ago.

[g] Diagnostic workup was referral to a positron emission tomography scan.

[h] The median follow-up was 33.7 months and only 161 (6.5%) participants had 5 or more years of follow-up. Baseline data are mainly reported

[I] Based on the LLP risk prediction model, participants with a 5% 5-year risk (or greater) of developing lung cancer were eligible.

[j] The NLST trial is completed. However, an cost effectiveness analysis of screening with LDCT based on the NLST data is planned.