Lung Cancer Screening
Clinical Practice Guideline

Approved by the
National Guideline Directors
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Developed by the National Lung Cancer Screening Guideline Development Team

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Recommendations

This evidence-based guideline is an adaptation of USPSTF's "Screening for Lung Cancer" guideline (2013).¹ The Guideline Development Team utilized AHRQ's evidence base to develop a Kaiser Permanente-specific recommendation and rationale. The rationale table is available in Appendix B.

A systematic review of the evidence for lung cancer screening was developed by AHRQ's Pacific Northwest Evidence Based Practice Center.² This review may be accessed through the following link: AHRQ evidence review.

AHRQ published a comparative modeling study, based on the National Lung Cancer Screening Trial (NLST) data, to determine an optimum lung cancer screening protocol.³ This study may be accessed through the following link: AHRQ lung cancer modeling.

Additional supporting documentation for the USPSTF Lung Cancer Screening guideline may be accessed through the following link: USPSTF lung cancer screening.

Lung Cancer Screening

- In asymptomatic persons aged 55 to 80 years who are at high risk* for lung cancer, consider annual screening for lung cancer with low-dose computed tomography (LDCT) (Weak recommendation)

- Discontinue screening once a person has not smoked for 15 years, or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery or radiation therapy. (Strong recommendation)

*High risk is defined as persons with a 30 pack-year or more history of smoking, and who currently smoke or have quit within the past 15 years.

Clinical Considerations:

Patient counseling should include a complete description of potential benefits and harms so individuals can decide whether or not to undergo LDCT screening.

- Evidence for screening individuals at lower risk of lung cancer (e.g., <30 pack-year smoking history with or without a family history of lung cancer or history of chronic lung disease) is insufficient. The relative benefits and harms of screening individuals with these risk factors are unknown.
- Advising smokers to stop smoking and referring them to a smoking cessation program is imperative because screening does not prevent lung cancer. Smoking cessation is the only intervention that can avoid increasing the risk of lung cancer.
• Annual LDCT screening may be inappropriate for patients with life-limiting comorbid conditions or poor functional status who would not be candidates for surgical treatment or radiation therapy.
• Among adults aged 75-80 years, there is a lack of direct evidence to inform relative benefits and harms.
• Lung cancer screening has been shown to prevent some deaths from lung cancer, but many deaths are not prevented.
  o In the largest study of lung cancer screening, only 50% of detected cancers were Stage I, for which treatment is most likely to be successful.
• Screening with annual LDCT may detect other incidental findings that can lead to additional tests and follow-up. Incidental findings occurred in 7.6% of NLST participants.
• The chances are 1 in 4 that initial LDCT will yield a positive result requiring follow-up testing; very few of these positive results will lead to a diagnosis of lung cancer.
  o Health insurance coverage for the cost of these follow-up tests may differ from the cost of the initial screening.
• The chances are 1 in 33 that an initial positive result will lead to an invasive biopsy.
  o The chance of complications from an invasive biopsy is low (0.5%).
Appendix A: National Lung Cancer Screening Guideline Development Team

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Click here for more information on the Kaiser Permanente National Guideline Program Process and Methodology for Systematic Development of Clinical Practice Recommendations.

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## Appendix B: Rationale

<table>
<thead>
<tr>
<th>TOPIC</th>
<th>Lung cancer screening with LDCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basis of Recommendation</strong></td>
<td>Lung cancer is the third most common type of cancer and the most common cause of cancer-related death in both men and women in the United States. The 5-year survival rate in cases detected when the disease is localized is 53.5%; this is compared with 26.1% for regional (spread to regional lymph nodes) and 3.9% for distant (metastatic) disease. The National Lung Cancer Screening Trial (n=53,454) of high lung cancer risk participants found that low dose computed tomography (LDCT) compared with chest x-ray (CXR) conducted over three screens reduced relative lung cancer mortality by 20 percent (3.1 per 1000 persons over 6.5 years absolute mortality reduction) and relative all-cause mortality by 6.7 percent (4.6 per 1000 absolute mortality reduction). This is associated with a number needed to screen to prevent one lung cancer death (NNS) over 6.5 years of approximately 320. Two smaller (n=2472 and 5861) fair-quality European trials of high lung cancer risk participants did not detect a benefit associated with LDCT screening compared with no LDCT screening. Yet, these trials were inconclusive as they were underpowered to demonstrate key outcomes. The key potential harms associated with LDCT screening are the occurrence of false positive screening results in approximately 23% of exams, and any major complication associated with downstream invasive testing that may be performed. The incidence of major complications from screening was overall low in NLST (0.5%), though it was considerably higher among those who eventually received a diagnosis of lung cancer (11.6%). Other important harms associated with LDCT screening include psychological distress, incidental findings, and the potentially cancer-causing effects of repeated radiation exposure. Adverse psychosocial effects of screening appear to be temporary, however the distress associated with having a lung nodule may be severe and last as long as it takes to exclude a diagnosis of cancer, sometimes as long as 2-3 years. 7.6% of participants in NLST had incidental findings on LDCT, however they did not elaborate in descriptions</td>
</tr>
</tbody>
</table>

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about the harms associated with these findings. Although a potential for radiation-induced cancers due to long-term annual screening exists, there are no longitudinal studies clearly defining the magnitude of risk. Microsimulation modeling using a similar target population and screening protocol predicts the likelihood of radiation-induced cancers over 25 years of screening to be relatively small (0.8%). That being said, the most effective duration or frequency of lung cancer screening is not known. The balance of benefit and harm beyond 3 consecutive screenings with LDCT is uncertain.

Summary

Because of the 20% cancer-specific relative mortality reduction and the 6.7% all-cause relative mortality reduction seen in the National Lung Screening Trial (NLST), as well as the low incidence of major complications from the evaluation process, offering lung cancer screening for high-risk adults ages 55-80 is considered reasonable.

Overall, evidence quality is moderate; although the NLST is a high quality study, other published trials do not support this trial’s findings.

Variability of values and preferences is assumed to be moderate. Some patients may have significant comorbidities that might make them hesitate to undergo any invasive diagnostic procedures. Therefore some may be more immediately concerned about the potential physical harms of screening.

From the perspective of the health care delivery system, resource implications for this recommendation are significant, attributed to costs associated with further testing due to a high rate of false positive results.

Therefore, a weak recommendation to offer lung cancer screening to high-risk adults ages 55-80 is warranted.

We make a strong recommendation to discontinue screening when patients have quit smoking for 15 years, has limited life expectancy, or are unwilling/unable to undergo curative therapy.

It is reasonable to assume the net benefit of screening is reduced as risk decreases. The NLST did not include patients who had quit smoking for greater than 15 years; therefore it is unknown whether these patients would benefit from screening.
Persons with limited life expectancy would not benefit from screening, as they are likely to die first from other life-limiting conditions.

The benefits of screening is contingent on undergoing treatment with curative intent, therefore persons who will not undergo curative therapy should not be screened.

<table>
<thead>
<tr>
<th>Balance of desirable and undesirable effects</th>
</tr>
</thead>
</table>
| The potential benefits of targeted lung cancer screening with low dose CT (relative risk reduction of 20% (lung-cancer specific mortality) and 6.7% (all-cause mortality), outweigh the low potential for major complications from biopsy (<1%). Balancing the benefits of screening with downstream consequences of false positive results, including psychosocial distress, should be addressed in a shared decision making context.  

At the same time, a successful cancer screening program will minimize harms to participants. In NLST, major complications were infrequent in both groups (0.5% overall) and tended to be higher in individuals who were found to have lung cancer (11.6%) than in those who were not (0.1%). Major complications included those related to lung function (prolonged mechanical ventilation, respiratory failure or arrest), cardiovascular complications (myocardial infarction, congestive heart failure, cardiac arrest, and cerebrovascular accident), injury to a vital organ or vessel, and death. Notably, 16 participants in the LDCT group died within 60 days after an invasive procedure (ten of whom had lung cancer), as did ten (all with lung cancer) in the CXR group. It is not known if the procedure itself was the cause of death and deaths were not reported separately by procedure.  

Uncertainty about the balance of benefit and harm is highest for screening candidates ages 75-80. Estimates of benefit and risk for patients screening at age 75 or older are based solely on the mathematical modeling done for the USPSTF, or upon SEER estimates of lung cancer incidence and mortality in this age group. NLST participants were screened for only 3 years and were ineligible to enroll if they were older than 74 years (only 8.8% of participants were aged 70 years or older at enrollment). This population might also be at higher risk of complications from diagnostic procedures following positive LDCT; this is not captured in the modeling studies.  

Uncertainty regarding the balance of benefits and harms is moderate, based on moderate-quality evidence for efficacy of
screening, as well as poorly defined risk of screening for those 75-80 years, and for those with significant comorbidities.

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Overall quality: Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits and harms of screening</td>
<td>Benefits and harms of surgical resection in patients with Stage 1 NSCLC</td>
</tr>
</tbody>
</table>

### Quality of Evidence

<table>
<thead>
<tr>
<th>Category (overall assessment)</th>
<th>Outcome</th>
<th>Importance</th>
<th>#/study design</th>
<th>Assessment</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits (moderate quality)</td>
<td>Lung cancer mortality</td>
<td>critical</td>
<td>4 RCTs</td>
<td>Moderate quality</td>
<td>Inconsistency: One high-quality study; but no confirmation from smaller studies</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>critical</td>
<td>4 RCTs</td>
<td>Moderate quality</td>
<td>Inconsistency: One high-quality study; but no confirmation from smaller studies</td>
</tr>
<tr>
<td>Harms</td>
<td>False positive results (proxy for increased costs, anxiety, and potential increase in incidental findings)</td>
<td>important</td>
<td>13-RCTs/cohort</td>
<td>Very low</td>
<td>Inconsistency; Inclusion of observational studies</td>
</tr>
<tr>
<td>Complications from invasive procedures</td>
<td>Critical</td>
<td>1 RCT [NLST]</td>
<td>Moderate quality</td>
<td>Imprecision: low event rates</td>
<td></td>
</tr>
<tr>
<td>Radiation induced cancers</td>
<td>important</td>
<td>No evidence available</td>
<td>No evidence available</td>
<td>No evidence available regarding effects of long term radiation exposure on radiation induced cancers-predicted from microsimulation studies only</td>
<td></td>
</tr>
<tr>
<td>Serious harms due to follow-up of incidental findings</td>
<td>important</td>
<td>No evidence available</td>
<td>No evidence available</td>
<td>No evidence available regarding harms due to unnecessary follow-up of incidental findings. In some cases, follow-up of incidental findings may be beneficial.</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Category (overall assessment)</th>
<th>Outcome</th>
<th>Importance</th>
<th>#/study design</th>
<th>Assessment</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit</td>
<td>5 year survival in pts with stage 1 NSCLC getting surgical resection</td>
<td>important</td>
<td>7 cohort studies</td>
<td>Low quality</td>
<td>Observational study design</td>
</tr>
<tr>
<td>Harms</td>
<td>Mortality from surgery</td>
<td>important</td>
<td>4 cohort studies</td>
<td>Very low quality</td>
<td>Observational study design; imprecision</td>
</tr>
</tbody>
</table>

**Values and Preferences**

This recommendation places a high value on preventing lung-cancer mortality, and on the low risk of serious complications from biopsy procedures.

Values and preferences were derived by polling the GDT. Uncertainty regarding values and preferences is estimated to be high, as patients’ values and preferences are not directly assessed.

Variability of values and preferences is assumed to be moderate, as a substantial portion of diagnosed cancers will be identified at an advanced stage; as well, some patients may have significant comorbidities that might make them hesitate to undergo any invasive diagnostic procedures. Therefore some may be more immediately concerned about the potential physical harms of screening.

**Resource implications**

From the perspective of the health care delivery system, resource implications for this recommendation are significant. LDCT as a screening tool is expensive, and should be restricted to persons at significant risk for lung cancer.

Resources required for following up and investigating positive CT scans are also significant. In the NLST trial, the overall rate of positive CT screens after 3 screens is 24.2%. 39% of NLST participants in the CT screening arm had at least 1 positive screening test result after 3 rounds of screening. Among the positive screens in the CT group, 96.4% were false positive results (23.3% of all screens). Imaging was the most commonly performed diagnostic process, and invasive procedures were performed infrequently.
The number needed to screen with LDCT in this population over 3 years to prevent one death from lung cancer is 320 based on the NLST. This is favorable when compared to the number needed to screen for breast cancer of 1339 in women 50-59 years after 11-20 years of follow-up and colorectal cancer when screening with flexible sigmoidoscopy of 817.

In the future, externally validated risk calculators may allow more focused screening efforts on the highest risk patients, improving screening performance of LDCT and thereby cost effectiveness.
Appendix C: Criteria for Grading the Evidence

Table C-1. Criteria for Assigning Grades of Evidence for Each Outcome

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trial</td>
<td>High</td>
</tr>
<tr>
<td>Observational study</td>
<td>Low</td>
</tr>
<tr>
<td>Any other evidence</td>
<td>Very low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decrease grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious limitation to study quality</td>
<td>-1</td>
</tr>
<tr>
<td>Very serious limitation to study quality</td>
<td>-2</td>
</tr>
<tr>
<td>Important inconsistency</td>
<td>-1</td>
</tr>
<tr>
<td>Some uncertainty about directness</td>
<td>-1</td>
</tr>
<tr>
<td>Major uncertainty about directness</td>
<td>-2</td>
</tr>
<tr>
<td>Imprecise or sparse data</td>
<td>-1</td>
</tr>
<tr>
<td>High probability of reporting bias</td>
<td>-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increase grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong evidence of association:</td>
<td>+1</td>
</tr>
<tr>
<td>Significant RR of &gt;2 (&lt;0.5) based on consistent evidence from two or more observational studies, with no plausible confounders</td>
<td></td>
</tr>
<tr>
<td>Very strong evidence of association:</td>
<td>+2</td>
</tr>
<tr>
<td>Significant RR of &gt;5 (&lt;0.2) based on direct evidence with no major threats to validity</td>
<td></td>
</tr>
<tr>
<td>All plausible confounders would have reduced the effect</td>
<td>+1</td>
</tr>
</tbody>
</table>

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Table C-2. GRADE Levels of Evidence across outcomes

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

Table C-3: Determinants of strength of recommendation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance between desirable and undesirable effects</td>
<td>The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.</td>
</tr>
<tr>
<td>Costs (resource allocation)</td>
<td>The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted</td>
</tr>
</tbody>
</table>

Appendix D: Supporting Documentation

AMSTAR assessment
The Lead Team identified an AHRQ existing systematic review that was deemed to be of acceptable quality and relevant to a specific clinical question. The studies analyzed in the existing systematic review examine relevant populations, interventions, comparisons and outcomes as delineated in the clinical question and the AHRQ Key Questions and Analytical Framework was fully incorporated. Using the online modification of the AMSTAR systematic review assessment checklist, this systematic review is found to be of high quality. AMSTAR review
Appendix E: Analytic Framework

Figure 1 is an analytic framework that depicts the pathway that asymptomatic adults at average or high risk for lung cancer may experience during screening for lung cancer. The figure shows that adults who undergo screening for lung cancer may have early detection of lung cancer or harms related to screening. The figure shows the next steps in the pathway for those who have early detection of lung cancer, is receiving treatment for lung cancer and harms related to treatment. The pathway shows outcomes of interest after screening and treatment to be decreased mortality and morbidity.

Figure 1. Analytic Framework

Key Questions:

1. How effective is screening for lung cancer in reducing morbidity and mortality?
   a. How effective is screening in persons at average risk?
   b. How effective is screening in persons at higher risk for lung cancer (e.g., current or former smokers)?
   c. Does effectiveness differ by subgroup (e.g., sex, age, race, presence of comorbid conditions, and other lung cancer risk factors)?
2. What are the test characteristics (sensitivity, specificity, and predictive value) of screening tests for lung cancer?
   a. How do these test characteristics vary by lung cancer risk?
   b. How do test characteristics differ by subgroup (e.g., sex, age, and race)?
3. What are the harms associated with lung cancer screening, and are there ways to modify harms (e.g., unnecessary biopsies, radiation exposure, overdiagnosis, and psychosocial harms)?
4. How effective is surgical resection for the treatment of early (stage IA) non–small-cell lung cancer?
5. What are the harms associated with surgical resection of early (stage IA) non–small-cell lung cancer?
Appendix F: References

