



LOW DOSE SPIRAL COMPUTERIZED TOMOGRAPHY (LDCT) SCREENING FOR LUNG CANCER

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of low dose spiral computerized tomography (LDCT) as a modality for lung cancer screening. This is an update of the review conducted in 2000 for the Blue Shield of California Medical Policy Committee on Quality and Technology. The 2000 review concluded that there was not yet enough data to support use of LDCT. We are readdressing this question after publication of a large international study,¹ which was widely publicized in the lay press and renewed public interest.

BACKGROUND

In the United States in 2007, there will be an estimated 213,380 new cases of lung cancer and an estimated 160,300 deaths from this disease.² The five year survival rate for this disease is only about 15%.^{3,4} Most lung cancers are not localized when first detected, but early detection is mandatory to improve prognosis. When stage I cancers are resected, five year survival ranges between 40%- 70%.⁴

In the 1970s, four large-scale randomized controlled trials (RCT), involving a total of 37,000 men (mostly smokers), were performed to determine the value of routine screening for lung cancer by chest x-rays and/or sputum cytology.⁵⁻⁸ Unfortunately, these studies provided strong evidence that screening does not lead to a decreased death rate from lung cancer. As a result of these trials, none of the major cancer guideline organizations (the American Cancer Society, the National Cancer Institute and the U.S. Preventive Services Task Force) recommend routine screening for lung cancer in asymptomatic individuals. However, because follow-up of at least one of these studies has shown differential survival for those patients who had their early stage lung cancer resected surgically,⁹ and because of criticisms of the design of these studies, the National Institutes of Health (NIH) continues to investigate chest x-ray (CXR) for lung cancer screening as part of a large RCT, the Prostate, Lung, colorectal and Ovarian (PLCO) Cancer Screening Trial.^{10,11} In addition, since curable early cases of lung cancer are hard to visualize with conventional chest x-rays, investigators have turned to CT in the hopes of finding more cases at an early, resectable stage.^{3,4,12}

Low Dose Spiral (Helical) CT Scanning

In general, conventional chest CT is more sensitive for the detection of lung nodules (including cancers) than plain chest x-ray or whole lung tomography.^{13, 14} Conventional CT has not been used to screen for lung cancer, however, because of the x-ray exposure dose, the time-consuming interpretation necessary, the large number of false-positive scans and the lack of proven cost-benefit.¹⁴ However, because of its ability to continuously acquire data, the use of LDCT results in a shorter scanning time and a lower radiation exposure dose. Use of a spiral CT scanning performed at 120 kVp, tube current of 50 mA, 1 sec/rotation, 10 mm collimation, and a pitch of 2.0 (table speed of 10 mm/sec) permits the entire lung to be scanned with ease during a single breath-hold in virtually all patients.¹⁵ The LDCT used for screening requires less than 20 seconds of scanning time and does not require intravenous contrast injection.¹⁶

LDCT has been found by one group of investigators to be useful as a second step in patients screened for lung cancer with plain chest x-ray, particularly in finding small, early stage, peripheral lesions.¹⁷ In addition, Itoh et al (1998) reported a comparison of LDCT to conventional CT of the lung in ten healthy volunteers and in 110 patients. Conventional CT detected a total of 196 lesions in the 110 patients. LDCT detected 177 (90%) of the 196 nodules (87 [96%] of 91 lesions greater than 5 mm in diameter), 54 of 57 focal parenchymal opacities, and 15 of 15 cases with fibrotic changes. Most of the lesions missed were less than 5 mm in diameter.¹⁵ LDCT does involve a greater radiation exposure dose to the patient than conventional chest x-ray, though less radiation exposure dose than conventional CT.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Several Spiral (Helical) CT scanners have been approved for use. The ImageChecker (R2 Technology, Sunnyvale, CA) and the Syngo Lung Care CT (Siemens, Malvern, PA) are FDA approved CAD Systems.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words 'lung cancer', cross-referenced with the keywords 'screening' and 'CT'. The search was performed for the period from 1966 through January 2007. The bibliographies

of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

There have been eight peer-reviewed published studies of LDCT to screen for lung cancer to date. All eight of them have been with high risk or mixed risk screening populations. The earliest study was cross-sectional¹⁴; six of the subsequent seven were longitudinal cohort studies^{1, 18-22}, and the seventh was a randomized control trial (RCT) intended as a feasibility pilot study²³.

Level of Evidence: 2, 4, 5

TA Criterion 2 is not met

TA Criterion 3: The technology must improve the net health outcomes.

Benefit

The design, outcomes, and results of the eight published trials are detailed in the Table below. As described above, the earliest study, by Kaneko et al, was cross-sectional, assessing lung cancers seen on LDCT and comparing that number to the number seen on CXR in the same patients.¹⁴ This design allows for information about the prevalence of lung cancer seen by the two modalities, as well about the stage of those cancers diagnosed based on LDCT. Seven of the eight remaining studies were longitudinal cohort studies which did a baseline screening by LDCT and then follow-up screening, ranging from a single annual screen to screens every six months for five years.^{1, 18-22} This design allows for information about both the prevalence of lung cancer seen on LDCT and its ability to detect incident cancers over time. Two of these trials compared lung cancer detection rates on LDCT to that on CXR;^{20, 21} one trial compared outcomes to historical controls from the Mayo Lung Project,²² and three trials made no comparison at all.^{1, 18, 19} The eighth study was an RCT which randomized participants to receive either a LDCT or a CXR to screen for lung cancer at baseline and at one subsequent annual visit.²⁴ Although quite large, this trial was intended to study the feasibility of randomizing to the two modalities, and to assess the number of participants required in each arm of a future, larger RCT examining this question in order to see a clinically significant difference between the two groups.

Smoking is clearly the single most important risk-factor for lung cancer.²⁴ Given that lung cancer is uncommon in non-smokers, trials of screening tests should focus on those at highest risk (e.g. those with a significant smoking history). Of the eight studies, four included only smokers or past-smokers^{14, 18, 22, 23}; while the other four included a mixed-risk population, ranging from 46%-86% smokers.^{1, 19-21} The studies with high-risk only populations found a prevalence of lung cancer on LDCT (baseline screen) of 1.2%-2%, and an incidence of lung cancer on LDCT (follow-up/annual screens) of 0.6%-2%. The studies with mixed-risk populations found a prevalence of lung cancer on LDCT

of 0.42%-1.3%, and an incidence of lung cancer on LDCT of 0.1%-0.6%. The majority of lung cancers found on LDCT in all studies were Stage I, ranging from 53%-93% at the baseline screen.

Five of the studies reported on mortality. Sone et al reported lung cancer specific mortality after variable, relative short-term follow-up of 1.2-3.7 years. With only 60 cases, lung cancer mortality in this study was 3.3%.²¹ Sobue et al reported lung cancer specific five year mortality of 15% for their 36 cases.²⁰ Diedrich et al reported lung cancer specific mortality after variable follow-up of two to 40 months of 27% for their 11 cases.¹⁸ Swenson et al reported a mortality rate of 2.8 per 1000 years and compared it to the overall mortality in the Mayo Lung Project (intensively screened and less intensively screened) of 2.0 per 1000 years, demonstrating not much improvement.²² Henschke et al reported an estimated ten year lung cancer specific mortality (after an average of five years follow-up) of 20% for their 484 cases; they also estimated the ten year lung cancer specific mortality for those participants with Stage I cancers found on LDCT at 12%.¹ The RCT did not report on mortality.

The most recent study (Henschke et al), was a very large (n=31,567) international study which included mostly high risk smokers (83%), a smaller number of participants with second-hand smoke exposure (12%), and an even smaller number with occupational exposure to toxins such as asbestos (5%). Outside of an extensive protocol for follow-up of abnormal scans, which allowed the investigators to minimize unnecessary invasive procedures,^{16, 25} and formal adjudication of all cases, the design of this study was not substantially different from previous studies. This was a large cohort study with a baseline screen by LDCT, and a follow-up "annual" screen for most participants, with no comparison group. Thus, the results of this study are subject to all of the same potential biases as those of preceding studies.

Potential Biases

The desire to find a screening test for lung cancer which will catch the disease at an early, resectable stage is soundly based in the principles of screening.²⁶ Screening principles require that the disease for which we are screening be an important cause of morbidity or mortality, which lung cancer certainly is. It also requires, however, that the screening test leads to net benefit for the screened population, and in the case of lung cancer this means decreasing cancer-specific mortality while not increasing mortality from the test or resultant interventions themselves. It is not yet clear from the published literature on LDCT that screening, even in high risk only populations, reduces lung cancer specific mortality. In the study by Swenson et al, LDCT did not reduce mortality compared to historical controls. None of the other studies compared mortality rates for screened versus control populations; they only reported on mortality rates for their screened populations. While the Henschke et al study is promising in that they showed an estimated ten year mortality rate for early stage cancers that was much lower than if those cancers were

to go undetected and untreated, this was a subanalysis and there was no control group. It remains a concern with all of these studies that the detection of a high proportion of early stage lung cancers is a result of either lead-time or length-time bias.

In screening, lead-time is the time between when the diagnosis of a disease is made by the screening test and when the disease would have presented clinically. Lead-time bias occurs when survival is counted from the time of the diagnosis by the screening test, but is only measured in these cases. In other words, lead-time bias falsely increases survival time for those patients being screened by identifying the disease earlier than it would have otherwise been identified, but not increasing actual survival from the disease. Thus, even if the screening is ineffective in increasing survival, making an earlier diagnosis will add lead-time to the survival measured for those patients with disease. Lead-time bias can be avoided by measuring mortality (or survival) among all screened and control subjects, not just measuring the mortality rate from diagnosis for cases (those with disease).²⁷

In addition, there are concerns regarding possible length-time bias. Length-time bias occurs when the disease being detected by a screening test has a more indolent natural history than disease that goes undetected by the screening test.²⁷ In other words, in the case of LDCT screening for lung cancer, the majority of cancers detected have been small, peripheral disease. It is possible, that this presentation represents a more indolent variation of disease than cancers not detected by screening, and thus cases diagnosed by LDCT would have lower mortality to begin with. Over-diagnosis bias is also of concern; in this scenario, some of the “disease” being diagnosed by the test is not really disease at all. Again, the best way to avoid length-time and over-diagnosis biases is to randomize participants to screening and control groups, and then compare the prognosis of all cases – those occurring in the screened group and those occurring in the control group.²⁷

Lastly, is the concern for volunteer bias. Individuals who volunteer to participate in a screening trial may be inherently different (healthier) than those who do not. They may have healthier habits, better access to healthcare, and different education or income levels. All of these differences could lead to a better prognosis for those participants, making it appear - in a study without a similar comparison group - that it is the screening test leading to a better outcome, when really the better outcome is inherent to the patient population being studied.²⁷

In the case of LDCT screening for lung cancer, only Swensen et al have measured mortality for a screened population compared to historical controls, and they found no significant mortality difference.²² Henscke et al, along with all of the previous studies, report a cumulative mortality rate only for cases; and while their findings state that more early stage disease is found on LDCT and that it appears that those with early stage disease have a lower mortality rate are promising, these results may be subject to lead-time and/or length-time bias. We are aware of one



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large National Cancer Institute (NCI) sponsored RCT ongoing to answer the question of mortality benefit from LDCT screening for lung cancer. This trial, the National Lung Screening Trial (NSLT), has completed recruitment of 50,000 current, or former, smokers at 30 sites across the United States. Participants were randomized to LDCT or CXR as a screening modality. The study was designed with the power to detect a 20% mortality benefit from LDCT screening.²⁸

Potential Harms

The studies which have included only high risk populations (current or former smokers), have found a high rate of non-calcified nodules >4mm on LDCT baseline screening, ranging from 10%-43%.^{14, 18, 22, 23} Of these, up to 93% are false positive tests.²² All of these nodules require follow-up, at a minimum by conventional CT, and at a maximum by surgical biopsy. Henschke et al have shown that it is possible to avoid much of the most invasive follow-up by following a complex, standardized protocol.¹ However, none of this follow-up is completely without risk – surgery, of course, carries risks of bleeding, infection, and death, but even a follow-up conventional CT carries some risk of increased radiation exposure and increased anxiety.²⁹ The published literature to date has not adequately assessed these long-term risks.

In addition, the adverse effects of higher radiation exposure due to the LDCT itself, particularly if repeated at a regular interval are unknown.³⁰ One researcher estimates that if 50% of all current and former smokers in the U.S. age 50-75 years old underwent annual LDCT screening for lung cancer, the radiation exposure from the screening tests themselves would result in a 1.8% increase in lung cancer cases.³¹ It remains unclear from current studies how much benefit is really accrued by repeat annual screens, or if a longer screening interval would be most beneficial.

TA Criterion 3 is not met.

Table. Design and Results of English Language Published Studies of LDCT for Lung Cancer Screening

Study	Population	Design	Comparison	Outcome	Results
Kaneko et al 1996 ¹⁴	1,369 high risk screening population 90% male Age 38-83 All smokers	Cross-sectional Combined data for baseline screen and up to 3 additional bi-annual screen	CXR – same participants	Positive exam Lung cancer diagnosis Detection on CXR Stage	588 positive CT 15 (0.43%) lung cancer cases 11 (73%) not visible on CXR 14/15 (93%) Stage I
Sone et al 1998, 2001 ^{21, 32}	5,483 screening population 54% male age 40-74 46% smokers	Longitudinal Baseline screen Annual screen x 2 subsequent years	CXR – same participants	Suspicious nodule Lung cancer diagnosis Detection on CXR Stage Mortality at follow-up	<u>Baseline screen (n= 5,483)</u> 279 (5.1%) suspicious nodules; 23 cancers (0.42%) <u>Year 1 annual screen (n=4,425)</u> 178 (3.9%) suspicious nodules; 27 cancers (0.61%) <u>Year 2 annual screen (n=3,878)</u> 136 (3.5%) suspicious nodules; 10 cancers (0.26%) 67% not visible on CXR (retrospectively) 53/60 (88%) cases Stage I <u>1.2-3.7 years f/u:</u> All cause mortality 5/60 = 8.3% Lung cancer mortality 2/60 = 3.3%
Sabue et al 2002 ²⁰	1,611 screening population 88% male age 40-79 86% smokers	Longitudinal Every 6 month screening for up to 5 years (all underwent at least 2 screens)	CXR; Sputum cytology – same participants	Positive test Lung cancer diagnosis Stage 5-year mortality	<u>Baseline screen (n=1,611)</u> 186 positive CT 77% not visible on CXR 96% not detected on sputum cytology 14 lung cancer cases (0.87%) 1 case found only on sputum cytology



					<p>Total cases found on CT: 13 (0.81%) 10/13 (77%) Stage I</p> <p><u>Repeat screens (n=7,891 over 5 yrs)</u> 721 positive CT 88% not visible on CXR 99% not detected on sputum cytology</p> <p>22 lung cancer cases (0.28%) 3 cases found only on sputum cytology Total cases found on CT: 19 (0.24%) 15/19 (79%) Stage I</p> <p><u>5-year mortality for all cases (n=36)</u> All cause mortality = 29% Lung cancer mortality = 15% Diagnosed at baseline screen = 24% Diagnosed at repeat screen = 30%</p>
Nawa et al 2002¹⁹	7,956 screening population 79% male age 40-69 77% smokers	Longitudinal Baseline screen Annual screen x 1 subsequent year	No comparison	Positive test = non- calcified pulmonary nodule ≥ 8mm Lung cancer diagnosis Stage	<p><u>Baseline Screen (n=7,956)</u> 541 positive tests requiring detailed CT 64 required invasive follow-up 36 (0.45%) cases of lung cancer 31/36 (85%) Stage I</p> <p><u>Annual Screen (n=5,568)</u> 148 positive tests requiring detailed CT 7 required invasive follow-up 4 (.07%) cases of lung cancer 4/4 (100%) Stage I</p>
Diedrich et al 2002¹⁸	817 high risk screening population 72% male Age 40-79	Longitudinal Baseline screen Follow-up screening x 2 years for patients	No comparison	Initial positive test = non-calcified pulmonary nodule Follow-up positive test = ≥ 10 mm and read	<p><u>Baseline Screen (n=817)</u> 350 initial positive test 29 follow-up positive test 12 underwent biopsy immediately 10 (1.2%) cases of lung cancer (with 12</p>



	All smokers; 45 pack year median hx (range 20-166)	with morphologically benign nodules found at baseline		as likely malignant on follow-up thin-section low dose CT Lung cancer diagnosis Mortality	tumors) 7/12 (58%) Stage I <u>2-year Follow-up Screen (n=17)</u> 1 grew at 24 months, biopsied 1 case Stage I lung cancer <u>2-40 months f/u:</u> All cause mortality 4/11 = 36% Lung cancer mortality 3/11 = 27%
Swensen et al 2002, 2003, 2005 ^{22, 33, 34}	1520 high risk screening population 52% male Age 50-85 All smokers ≥ 20 pack year history; 45 pack year median (range 20-230)	Longitudinal Baseline screen Annual screen x 4 subsequent years	Comparison to historical controls from Mayo Lung Project (MLP) – subset of men > 50 with 4 years of follow-up	Positive test = non-calcified pulmonary nodule False positive test rate Lung cancer diagnosis Stage Mortality	<u>Baseline Screen (n= 1520)</u> 749 nodules any size 404 nodules > 4mm 96% false positive rate for nodule any size 93% false positive rate for nodule > 4mm 31 (2%) lung cancers 22 (76%) of non-small cell cancers Stage I <u>Annual Screens (n=1490)</u> 773 nodules any size 378 nodules > 4mm 96% false positive rate for nodule any size 93% false positive rate for nodule > 4mm 32 (2%) lung cancers 17 (61%) of non-small cell cancers Stage I <u>Comparison to Mayo Lung Project</u> Mortality: CT screened 2.8 per 1000 person-years MLP overall 2.0 per 1000 person-years



<p>Gohogan et al 2004, 2005^{23, 24}</p>	<p>3,318 high risk screening population 59% male Age 55-74 All smokers ≥ 30 pack year history; 54 pack year median</p>	<p>RCT pilot feasibility study – randomized to CXR (1,658) versus LDCT (1,660) Baseline screen Annual screen x 1 subsequent year</p>	<p>CXR – randomized comparison group</p>	<p>Positive test = non-calcified pulmonary nodule ≥ 4mm or any other finding radiologist considered suspicious of malignancy Lung cancer diagnosis Stage Adherence to study protocol</p>	<p><u>Baseline Screen (n=3,318)</u> 325 positive LDCT 30 (1.9%) lung cancer cases 16 (53%) Stage I</p> <p>152 positive CXR 7 (0.45%) lung cancer cases 6 (86%) Stage I</p> <p><u>Annual Screen (n=2,656 negative at baseline)</u> 221 positive LDCT 8 (0.57) lung cancer cases 2 (25%) Stage I</p> <p>93 positive CXR 9 (0.68) lung cancer cases 2 (22%) Stage I</p> <p><u>Adherence to randomization & follow-up</u> LDCT screen completion: Baseline 96% Annual 86% Receipt of CXR after negative annual exam: 20%</p> <p>CXR screen completion: Baseline 93% Annual 80% Receipt of spiral CT after negative annual exam: 2.2%</p>
<p>Henschke et al, 1999, 2001, 2006^{1, 16, 35}</p>	<p>31,567 mixed risk population ?% male Age 40-85</p>	<p>Longitudinal Baseline screen and annual screen x 1</p>	<p>No comparison</p>	<p>Positive test = at baseline solid pulmonary nodule ≥ 5mm or nonsolid</p>	<p><u>Baseline Screen (n= 31,567)</u> 4,186 positive test 405 (1.3%) lung cancers</p>



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	<p>Mixed population 83% smokers 12% exposure to 2nd hand smoke 5% occupational exposure Median 35 pack year history (range 0-141)</p>	<p>subsequent year</p>		<p>nodule \geq 8mm; at annual new non- calcified nodule Lung cancer diagnosis Stage Estimated 10-year mortality for stage I cancers</p>	<p><u>Annual Screen (n=27,456)</u> 1,460 positive test 74 (0.27%) lung cancers 5 cases interim diagnoses of lung cancer 412/484 (85%) Stage I Estimated 10-year lung cancer specific mortality (average follow-up 5 years) All cancers 20% For Stage I cancers 12%</p>
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TA Criterion 4: The technology must be as beneficial as any established alternatives.

There are no established alternatives for lung cancer screening. As noted above in the background section, past trials of sputum cytology and CXR have failed to show a mortality benefit. Because of criticisms of the design of the prior negative trials, particularly the lack of power to detect less than 50% reduction in lung cancer mortality, the NIH is currently sponsoring a large cancer screening RCT - the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial – which is examining the impact of CXR screening on lung cancer mortality.¹¹ In turn, the NLST is comparing LDCT to CXR, and thus if CXR is eventually established as a lung cancer screening modality, this study will answer the question of whether LDCT is as or more beneficial than CXR.²⁸

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Because LDCT as a screening modality for lung cancer has not yet been established in clinical trials as providing a mortality benefit, we cannot evaluate whether any improvement is attainable outside the investigational setting. However, if a mortality benefit is established, it is likely that with appropriate guidelines for reading the LDCT and appropriate follow-up guidelines, this will be attainable outside the investigational setting.²⁹

TA Criterion 5 is not met.

CONCLUSION

In summary, the published literature on the use of LDCT to screen for lung cancer in high risk populations is promising, but not conclusive. None of the studies – even the most recent, large, international study – were designed to account for potential biases such as lead-time and length-time biases, and so cannot offer firm evidence that the ability of LDCT to detect small, early-stage cancers actually leads to decreased mortality. The one study which does compare mortality rates to a historical control did not find any survival advantage for those screened with LDCT. The risks of screening (radiation exposure, follow-up non-invasive and invasive procedures, anxiety) are potentially great, particularly if the benefits of screening are unproven. Thus, use of LDCT screening cannot yet be recommended outside of the investigational setting. We await the results of the NSLT and any subsequent guidelines on reading and follow-up of positive LDCT screening exams.



RECOMMENDATION

It is recommended that the use of LDCT as a screening test for lung cancer does not meet CTAF criteria 2-5 because it is unclear, as of yet, if it reduces lung cancer specific mortality.

The CTAF panel voted unanimously to accept the recommendation as written.

February 28, 2007

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted a review of this technology.

Centers for Medicare and Medicaid Services (CMS)

There is not a National Coverage Determination specific to the use of this technology for screening for lung cancer.

American Cancer Society (ACS)

The ACS "current opinion is similar to the USPSTF, i.e., that there is insufficient evidence to recommend for or against lung cancer screening." An ACS representative provided testimony at the meeting.

California Radiological Society (CRS)

The CRS provided an opinion which noted that they believe that more research and evaluation is necessary. A representative was not available to participate at the meeting

California Thoracic Society (CTS)

The CTS was invited to provide an opinion and to send a representative to participate at the meeting.

Association of Northern California Oncologists (ANCO)

ANCO endorses the statement of the International Association for the Study of Lung Cancer (IASLC - <http://www.iaslc.org/documents/screeningstatement2006.doc>). A representative was not available to attend the meeting.

Medical Oncology Association of Southern California (MOASC)

MOASC was invited to provide an opinion and to send a representative to participate at the meeting.

American College of Chest Physicians (ACCP)

The ACCP guidelines regarding Lung cancer are available at: http://www.chestjournal.org/content/vol123/1_suppl/.
A representative was not available to participate at the meeting.

ABBREVIATIONS USED IN THIS ASSESSMENT:

LDCT: Low dose spiral computerized tomography

NSLT: National Lung Screening Trial

NCI: National Cancer Institute

RCT: Randomized controlled trials

NIH: National Institutes of Health

CXR: Chest x-ray

PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

DARE: Database of Abstracts of Reviews of Effects

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