Controversies and discoveries in lung cancer screening of smokers

D.B. Flieder, M.D.
Fox Chase Cancer Center
Philadelphia, PA

Lung cancer screening in smokers

Chest CXR screening in the 1950's through 2011

- Philadelphia
- Great Britain
- Czechoslovakia
- Mayo Clinic
- Johns Hopkins
- Memorial Sloan Kettering

PLCO cancer screening trial

Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality. JAMA 2011;306(17):1865–73.

Lung cancer screening in smokers

Uncontrolled chest CT screening in the 1990's and 2000's

- ELCAP
- University of Münster
- Antilung Cancer Association Project
- Mayo Clinic
- …

Lung cancer screening in smokers

Randomized controlled chest CT screening 2000's and 2010's

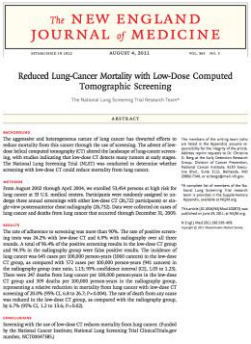
- NLST
- DANTE
- DLCST
- ITALUNG
- LUSI
- Dépiscan
- NELSON
- UKLS

Lung cancer screening in smokers

Country/name	Patients in LDCT arm (n)	Patients in control arm (n)	Study design	High-risk group	Age	Gender Male (%)	Selection	Incidence screen rounds	Begin / end intervention / end follow-up
Netherlands, Belgium/NELSON[10]	7557	7557	LDCT vs. no intervention	(ex-)Smokers > 30 pky	50–75		PB	Yr 2, yr 4 and yr 5.5	2003/2009/2015
Denmark[61]	2052	2052	LDCT vs. no intervention	(ex-)Smokers > 30 pky	50–70	59%	JA	Yr 2, 3, 4, 5	2004/2010/2016
Italy/ITALUNG[29,54,74]	1593	1613	LDCT vs. no intervention	(ex-)Smokers > 30 pky	55–69	69%	HC	Yr 2, 3, 4	2004/2015 / N/A
Italy/DANTE[87]	1276	1198	LDCT vs. chest X-ray	(ex-)Smokers > 20 pky	60–74	100%	JA	Yr 2, 3, 4	
Germany[88]/LUSI	1254	1251		(ex-)Smokers > 30 pky	50–69	N/A	PB	Yr 2, 3, 4, 5	2007/2013/2014
France (pilot)/ Depiscan[89]	375	390	LDCT vs. chest X-ray	>30 pky Smokers 64%, former smokers 36%	50–75	71%	HC	N/A	
US NLST[17] /ACRIN[13]	26722	26732	LDCT vs. chest X-ray	Heavy smokers and ex-smokers <15 years ago	55–74	59%	PB JA HC	N/A	2002/2009/2011

PB, population-based selection with mass mailing, HC, selection through healthcare, JA, journal advertisement, PE, physical examination. NB:1:26 Netherlands-Belgium Lungkanker Screening Onderzoek, ITALUNG, Italian lung cancer screening, DANTE, North Italian RCT lung cancer screening study, LUSI, German component of the European trial on the efficacy of multidose CT for the early detection of lung cancer, Depiscan, French randomized pilot trial of lung cancer screening comparing low-dose CT scan and chest X-ray, LLS, Lung Cancer Screening Study NLST, National Lung Cancer Screening Trial (10 sites), pky, pack years, N/A, not available.

Lung cancer screening in smokers



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

The aggressive and heterogeneous nature of lung cancer has thwarted efforts to reduce mortality from this cancer through the use of screening. The advent of low-dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages. The National Lung Screening Trial (NLST) was conducted to determine whether screening with low-dose CT could reduce mortality from lung cancer.

METHODS

From August 2002 through April 2004, we enrolled 53,454 persons at high risk for lung cancer at 33 U.S. medical centers. Participants were randomly assigned to one of two screening arms, stratified according to sex, smoking history, and study site. Participants in the intervention arm underwent three annual screenings with either low-dose CT (26,722 participants) or standard chest posteroanterior (PA) radiography (26,732). Data were collected on cases of lung cancer and deaths from lung cancer that occurred through December 31, 2009, and were used in this analysis. The study was stopped after a mean follow-up period of 6.5 years. We calculated the rate of lung-cancer mortality in the two study groups and compared the rates by a Poisson regression model. All CT scans and chest X-ray films were read by radiologists, and we compared the rates of detection, diagnostic follow-up, complications, and ancillary findings between the two screening modalities.

RESULTS

The rate of adherence to screening was more than 90%. The rate of positive screening was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.9% in the radiography group were false positive results. The incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group, as compared with 572 cases per 100,000 person-years (941 cancers) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.05 to 1.23). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The rate of death from any cancer was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 14.6; P=0.03).

CONCLUSIONS

Screening with the use of low-dose CT reduces mortality from lung cancer. (Funded by the National Cancer Institute; National Lung Screening Trial ClinicalTrials.gov number, NCT00047385.)

The members of the writing team (who are listed in the Appendix) assume responsibility for the accuracy and integrity of the data and for the analysis. Dr. Christine D. Berg at the Early Detection Research Group, Cancer Prevention and Control, National Cancer Institute, 6120 Executive Blvd., Suite 3115, Bethesda, MD 20892-7405, or at bergc@mail.nci.nih.gov.

*A complete list of members of the National Lung Screening Trial Research Team is provided in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1102873) was published on June 29, 2011, at NEJM.org.

N Engl J Med 2011;365:395-409.
Copyright © 2011 Massachusetts Medical Society.

Lung cancer screening in smokers

Lung cancer screening in smokers

NLST

53,454 subjects from 33 US centers

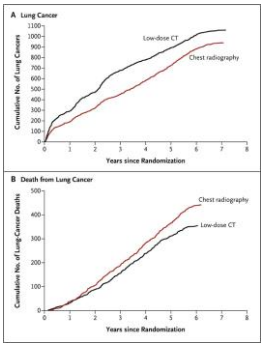
Ages 55-74

At least 30 pack years of smoking
current smokers or quit within past 15 years

3 annual screenings with 6 years of follow-up
CXR or LDCT

Primary endpoint---lung cancer mortality (20% reduction)

Lung cancer screening in smokers



Lung cancer screening in smokers

NLST conclusions

20% relative mortality reduction compared with CXR
absolute risk reduction of 3 per 1,000 individuals

Absolute risk of death from lung cancer
LDCT group 1.4% vs CXR group 1.7%

Lung cancer screening in smokers

Differing guidelines

ACS
ACCP
ASCO
ATS
IASLC

USPSTF

NCCN
AATS

AAFP
ESMO

Lung cancer screening in smokers

Great result!

USPSTF assessment

Grade B recommendation

"high certainty that the net benefit is moderate
or
moderate certainty that the net benefit is moderate
to substantial"

Lung cancer screening in smokers

Great result!

AHRQ commissioned CISNET to model effect of LDCT for USPSTF recommendations!

5 models ran 576 scenarios—8 most efficient

Ages 55-80 for up to 15 years after tobacco cessation

Lung cancer screening in smokers

TO: Administrative File: CAG-00439N

FROM: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Acting Deputy Director, Coverage and Analysis Group
Lead Medical Officer

Lori Ashby
Acting Director, Division of Medical and Surgical Services

Jamie Hermansen, MPP
Lead Health Policy Analyst

Joseph Dolph Hutter, MD, MA
Medical Officer

SUBJECT: Final National Coverage Determination on Screening for Lung Cancer with Low Dose Computed Tomography (LDCT)

DATE: February 5, 2015

I. Decision

The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to add a lung cancer screening counseling and shared decision making visit, and for appropriate beneficiaries, annual screening for lung cancer with low dose computed tomography (LDCT), as an additional preventive service benefit under the Medicare program only if all of the following criteria are met:

Beneficiary eligibility criteria:

- Age 55 – 77 years;
- Asymptomatic (no signs or symptoms of lung cancer);
- Tobacco smoking history of at least 30 pack-years (one pack-year = smoking one pack per day for one year; 1 pack = 20 cigarettes);
- Current smoker or one who has quit smoking within the last 15 years; and
- Receives a written order for LDCT lung cancer screening that meets the following criteria:

Lung cancer screening in smokers

- *For the initial LDCT lung cancer screening service:* a beneficiary must receive a written order for LDCT lung cancer screening during a lung cancer screening counseling and shared decision making visit furnished during any appropriate visit with a physician (meaning a doctor of medicine, doctor of osteopathy, doctor of dentistry, or doctor of podiatry), or a qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in §1861(aa)(5) of the Social Security Act). A lung cancer screening counseling and shared decision making visit must include the following elements (and is appropriately documented in the beneficiary's medical records):
  - Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;
  - Counseling on the benefits and harms of performing the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
  - Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
  - Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; and, for those who are current cigarette smokers, smoking cessation, if appropriate, furnishing of information about tobacco cessation interventions; and
  - If appropriate, the furnishing of a written order for lung cancer screening with LDCT.
- *For subsequent LDCT lung cancer screenings:* the beneficiary must receive a written order for LDCT lung cancer screening, which may be furnished during any appropriate visit with a physician (meaning a doctor of medicine, doctor of osteopathy, doctor of dentistry, or doctor of podiatry), or a qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in Section 1861(aa)(5) of the Social Security Act). If a physician or qualified non-physician practitioner elects to furnish a beneficiary with a written order for LDCT lung cancer screening during a subsequent lung cancer screenings with LDCT, the visit must meet the criteria described above for a counseling and shared decision making visit.
- Written orders for both initial and subsequent LDCT lung cancer screenings must contain the following information, which must also be appropriately documented in the beneficiary's medical records:
  - Beneficiary date of birth;
  - Actual pack - year smoking history (number);
  - Current smoking status, and for former smokers, the number of years since quitting smoke;
  - Statement that the beneficiary is asymptomatic (no signs or symptoms of lung cancer); and
  - National Provider Identifier (NPI) of the ordering practitioner.

Reading radiologist eligibility criteria:

- Board certification or board eligibility with the American Board of Radiology or equivalent organization;
- Documented training in diagnostic radiology and radiation safety;
- Involvement in the supervision and interpretation of at least 300 chest computed tomography acquisitions in the previous year;
- Documented participation in continuing medical education in accordance with current American College of Radiology standards; and
- Furnish lung cancer screening with LDCT in a radiology imaging facility that meets the radiology imaging facility eligibility criteria below.

Radiology imaging facility eligibility criteria:

- Performs LDCT with volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy (milligray) for standard size patients (defined to be 5' 7" and approximately 155 pounds) with appropriate reductions in CTDIvol for patients of smaller and larger sizes, as defined by the ACR-AAPM Practice Guideline;
- Utilizes a standardized lung nodule identification, classification and reporting system;
- Makes available smoking cessation interventions for current smokers; and

Lung cancer screening in smokers

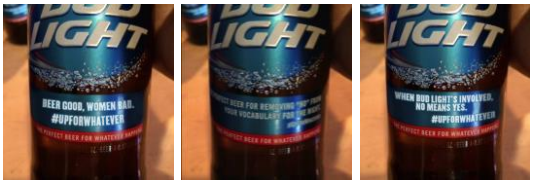
All CMS-approved registries must have the capacity and capability to collect data from any Medicare-eligible imaging facility/department that furnishes lung cancer screening with LDCT, with a catchment area that includes all 50 States, United States Territories, and the District of Columbia. CMS will evaluate each entity interested in participating as a CMS-approved registry to determine if they are capable of meeting the registry and data collection requirements outlined in this national coverage determination, including:

a. Establishment of a steering committee and a governance board for oversight of the registry;
b. Registry management plan, including identification of key personnel;
c. Operational plan and framework that describes mechanisms for collection and submission of data from imaging facilities to the registry;
d. Registry catchment area;
e. Mechanisms for the submission of registry data to CMS electronically;
f. Mechanisms to collect information (e.g.; HICN) in order to permit linkage of registry data with external databases (e.g. Medicare claims data sets);
g. Description of data management and data quality review methods, including validation;
h. Use of CMS-approved standardized data dictionary;
i. Mechanisms for submitting a list of facilities participating in the registry to CMS; and
j. Quality assurance plan.

To apply to function as a CMS-approved registry, interested entities must submit a letter of interest along with detailed supporting information about how the interested entity is able to meet the requirements outlined in this national coverage determination to the following address or via email to caginquiries@cms.hhs.gov.

Lung cancer screening in smokers

Real controversy



Lung cancer screening in smokers

Controversies

Generalizability to broader US population

Participants

Hospitals

Bach PB, Gould MK. When the average applies to no one: Personalized decision making about the potential benefits of lung cancer screening. Ann Intern Med 2012;157:571-3.

Lung cancer screening in smokers

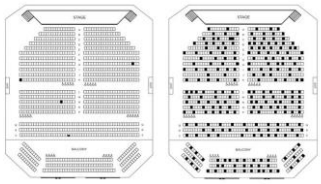
Controversies

Radiation exposure

Lung cancer screening in smokers

Controversies

Psychological distress



Lung cancer screening in smokers

Controversies

Overdiagnosis

Lung cancer screening in smokers

Table 1 Number of Cancers per Year by Histologic Analysis (Low-Dose Computed Tomography [LDCT] and Chest Radiography [CXR] Arms)

Histologic Subtype	Study Year Associated With First Confirmed Lung Cancer, No. (%)										
	T_0	T_1	T_2	Subtotal T_0-T_2	T_3	T_4	T_5	T_6	T_7	Subtotal T_3-T_7	Total T_0-T_7
LDCT											
All NSCLC, including BAC and NOS	273 (91.9)	165 (88.7)	204 (86.1)	642 (89.2)	47 (67.1)	83 (77.6)	106 (79.7)	47 (81.0)	1 (100.0)	284 (77.0)	926 (85.0)
BAC only	38 (12.8)	30 (16.1)	29 (12.2)	97 (13.5)	1 (1.4)	5 (4.7)	6 (4.5)	2 (3.4)	0	14 (3.8)	111 (10.2)
Small cell	20 (6.7)	21 (11.3)	27 (11.4)	68 (9.4)	20 (28.6)	21 (19.6)	26 (19.5)	8 (13.8)	0	75 (20.3)	143 (13.1)
Carcinoid	2 (0.7)	0	3 (1.3)	5 (0.7)	1 (1.4)	0	0	0	0	1 (0.3)	6 (0.6)
Unknown	2 (0.7)	0	3 (1.3)	5 (0.7)	2 (2.9)	3 (2.8)	1 (0.8)	3 (5.2)	0	9 (2.4)	14 (1.3)
Total	297 (100.0)	186 (100.0)	237 (100.0)	720 (100.0)	70 (100.0)	107 (100.0)	133 (100.0)	58 (100.0)	1 (100.0)	369 (100.0)	1089 (100.0)
CXR											
All NSCLC, including BAC and NOS	164 (85.0)	110 (82.7)	118 (81.4)	392 (83.2)	92 (80.0)	123 (86.0)	131 (78.9)	53 (73.6)	2 (100.0)	401 (80.5)	793 (81.8)
BAC only	8 (4.1)	3 (2.3)	7 (4.8)	18 (3.8)	5 (4.3)	3 (2.1)	10 (6.0)	0	0	18 (3.6)	36 (3.7)
Small cell	27 (14.0)	20 (15.0)	25 (17.2)	72 (15.3)	22 (19.1)	19 (13.3)	34 (20.5)	16 (22.2)	0	91 (18.3)	163 (16.8)
Carcinoid	1 (0.5)	1 (0.8)	0	2 (0.4)	0	0	0	1 (1.4)	0	1 (0.2)	3 (0.3)
Unknown	1 (0.5)	2 (1.5)	2 (1.4)	5 (1.1)	1 (0.9)	1 (0.7)	1 (0.6)	2 (2.8)	0	5 (1.0)	10 (1.0)
Total	193 (100.0)	133 (100.0)	145 (100.0)	471 (100.0)	115 (100.0)	143 (100.0)	166 (100.0)	72 (100.0)	2 (100.0)	498 (100.0)	969 (100.0)

Abbreviations: BAC, bronchioloalveolar cell carcinoma; NOS, not otherwise specified; NSCLC, non-small cell lung cancer. † Indicates study year, beginning with T_0 at baseline.

Patz Jr. EF, Pinsky P, Gatsonis G, et al. Overdiagnosis in Low-Dose Computed Tomography Screening for Lung Cancer. JAMA Intern Med 2014;172(2):269-74

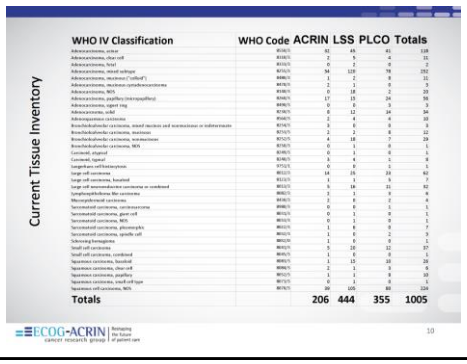
Lung cancer screening in smokers

Table 6. Histologic Type of Lung Cancers in the Two Screening Groups, According to Tumor Stage.*

Histologic Type	Total No. of Cancers	Stage of Cancer						
		IA	IB	IIA	IIB	IIIA	IIIB	IV
		number/total number (percent)						
Low-dose CT group								
Bronchioloalveolar carcinoma	110	83/110 (75.5)	6/110 (5.5)	3/110 (2.7)	1/110 (0.9)	1/110 (0.9)	8/110 (7.3)	8/110 (7.3)
Adenocarcinoma	380	173/376 (46.0)	48/376 (12.8)	17/376 (4.5)	10/376 (2.7)	31/376 (8.2)	33/376 (8.8)	64/376 (17.0)
Squamous-cell carcinoma	243	90/239 (37.7)	35/239 (14.6)	9/239 (3.8)	16/239 (6.7)	26/239 (10.9)	32/239 (13.4)	31/239 (13.0)
Large-cell carcinoma	41	17/41 (41.5)	4/41 (9.8)	0/41	3/41 (7.3)	7/41 (17.1)	5/41 (12.2)	5/41 (12.2)
Non–small-cell carcinoma, other†	131	38/127 (29.9)	10/127 (7.9)	1/127 (0.8)	5/127 (3.9)	16/127 (12.6)	17/127 (13.4)	40/127 (31.5)
Small-cell carcinoma	137	8/133 (6.0)	1/133 (0.8)	5/133 (3.8)	3/133 (2.3)	17/133 (12.8)	27/133 (20.3)	72/133 (54.1)
Carcinoid	6	2/2 (100.0)	0/2	0/2	0/2	0/2	0/2	0/2
Unknown	12	5/12 (41.7)	0/12	0/12	0/12	1/12 (8.3)	0/12	6/12 (50.0)
Total	1060	416/1040 (40.0)	104/1040 (10.0)	35/1040 (3.4)	38/1040 (3.7)	99/1040 (9.5)	122/1040 (11.7)	226/1040 (21.7)
Radiography group								
Bronchioloalveolar carcinoma	35	17/35 (48.6)	1/35 (2.9)	1/35 (2.9)	2/35 (5.7)	3/35 (8.6)	5/35 (14.3)	6/35 (17.1)
Adenocarcinoma	328	83/326 (25.5)	42/326 (12.9)	17/326 (5.2)	12/326 (3.7)	29/326 (8.9)	29/326 (8.9)	114/326 (35.0)
Squamous-cell carcinoma	206	51/205 (24.9)	29/205 (14.1)	6/205 (2.9)	17/205 (8.3)	24/205 (11.7)	28/205 (13.7)	50/205 (24.4)
Large-cell carcinoma	43	9/42 (21.4)	5/42 (11.9)	1/42 (2.4)	1/42 (2.4)	10/42 (23.8)	7/42 (16.7)	9/42 (21.4)
Non–small-cell carcinoma or other†	158	20/155 (12.9)	9/155 (5.8)	3/155 (1.9)	5/155 (3.2)	24/155 (15.5)	24/155 (13.5)	70/155 (45.2)
Small-cell carcinoma	159	11/157 (7.0)	6/157 (3.8)	4/157 (2.5)	5/157 (3.2)	18/157 (11.5)	28/157 (17.8)	85/157 (54.1)
Carcinoid	2	2/2 (100.0)	0/2	0/2	0/2	0/2	0/2	0/2
Unknown	10	3/7 (42.9)	1/7 (14.3)	0/7	0/7	1/7 (14.3)	1/7 (14.3)	1/7 (14.3)
Total	941	196/929 (21.1)	93/929 (10.0)	32/929 (3.4)	42/929 (4.5)	109/929 (11.7)	122/929 (13.1)	335/929 (36.1)

* The denominators represent only cancers for which the stage was known.
† The 289 lung cancers in this category (in the two groups combined) included 28 adenosquamous carcinomas, 8 sarcomatoid carcinomas, 55 unclassified carcinomas, 1 anaplastic-type carcinoma, 1 carcinosarcoma, and 198 coded only as "non–small-cell carcinoma."

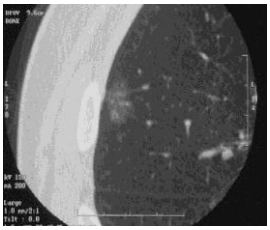
Lung cancer screening in smokers



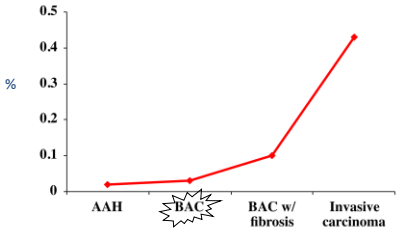
Lung cancer screening in smokers

Discoveries

Lung cancer screening in smokers

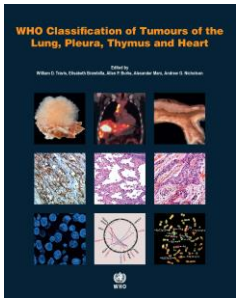


Lung cancer screening in smokers

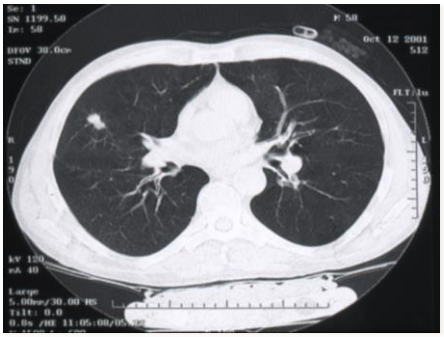


Aoyagi Y, Yokose T, Minami Y, et al. Accumulation of losses of heterozygosity and multistep carcinogenesis in pulmonary adenocarcinoma. Cancer Res 2001;61:7950-7954.

Lung cancer screening in smokers



Lung cancer screening in smokers



Lung cancer screening in smokers

Lung cancer screening in smokers

Lung cancer screening in smokers

Employing a smoker costs an additional $5,816 per year

Paying $800 for cessation is a great bargain!

CVS CAREMARK

Lung cancer screening in smokers

Lung cancer screening in smokers

Lung cancer screening in smokers

<u>Controversies</u>

Cost-effectiveness -- Quality-adjusted life year (QALY)

NLST

$81,000 per QALY

Women	$46,000 per QALY
Men	$147,000 per QALY
Current Smokers	$43,000 per QALY
Former Smokers	$615,000 per QALY
Highest risk	$32,000 per QALY
Lowest risk	$269,000 per QALY

Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National lung Screening trial. NEJM 2014;371:1793-802.