



Outcomes in the NLST

Health system infrastructure needs to implement screening

Denise R. Aberle, MD
Professor of Radiology and Bioengineering
David Geffen School of Medicine at UCLA



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- Grant support:

U01 CA196408 Integrated Molecular, Cellular and Imaging Characterization of Screen-detected Lung Cancer

PCORI Lung Nodule Surveillance Trial

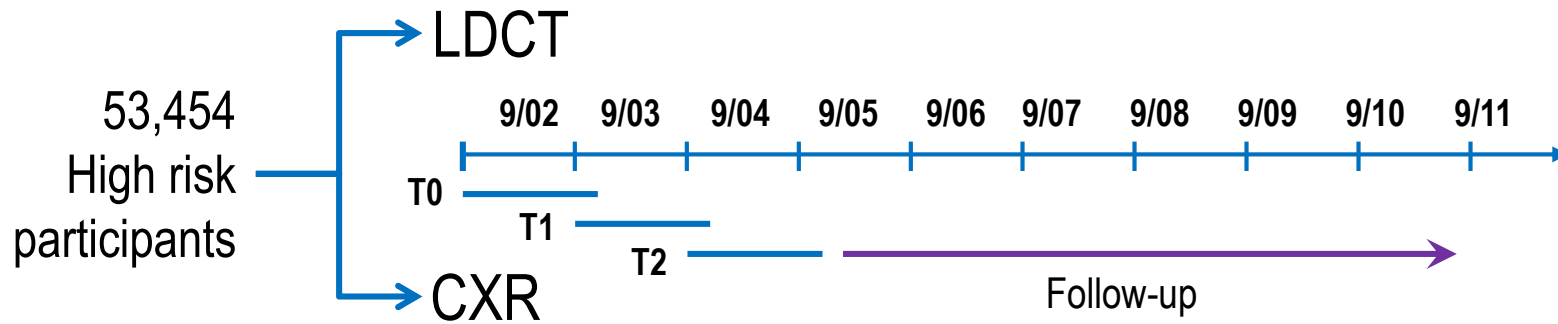
U01 CA037403 ECOG-ACRIN Early Detection and Diagnosis

R01 LM011333 RUMI: A Patient Portal for Retrieving Understandable Medical Information

T32 EB016640 Medical and Imaging Informatics Training Program

What have we learned & how do we translate this to practice?

- Eligibility
- Diffusion of screening across at-risk populations
- Standardized image acquisition & interpretation
- Data collection & longitudinal FU
- Smoking cessation



- 24% CT screens positive (nodule \geq 4 mm) | PPV \sim 4%
- Few complications, especially in those with false [+] screens: $<$ 0.1%
- 20% relative decrease in lung cancer-specific mortality
- 6.7% relative decrease in all-cause mortality
- NNS to prevent 1 death: 320
- Overdiagnosis estimated at 10-20%



- Eligibility criteria: Age 55-74 | ≥ 30 pack yrs | Current or former smoker
For former smokers: YSQ ≤ 15 years
- Ineligibility was infrequent in NLST

A. Age:

1. What is your date of birth? (mm-yyyy)

2. What was your age at your last birthday? years of age

B. Cigarette Smoking History:

3. Have you ever smoked cigarettes?
1 no
2 yes

4. At what age did you start smoking cigarettes?

5. Do you smoke cigarettes now?
1 no
2 yes (skip to Q7)

6. When was your last cigarette?
1 less than 6 months ago
2 6 months to 3.9 years ago
3 4 years to 9.9 years ago
4 10 years to 15 years ago
5 more than 15 years ago

7. For how many years total have you smoked cigarettes?

8. How many cigarettes smoked per day (on average)?

Referrals for ineligible patients is a *current* concern.

Risk to benefit ratio is unknown

Their screens are not a covered benefit



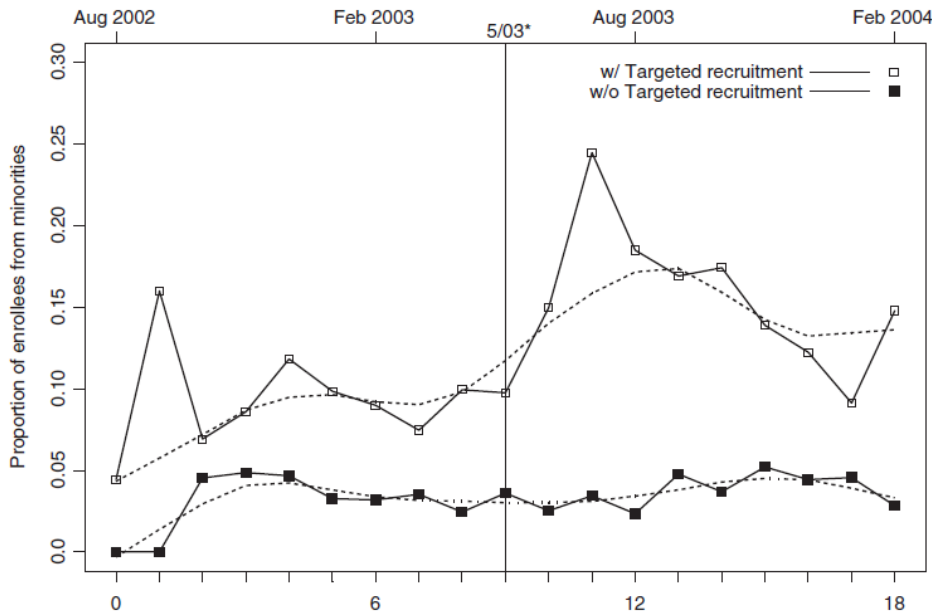
Goal: Enroll cohort representative of the eligible general population
Based on US Census Department's Tobacco Use Supplement 2002-2004

| Characteristic | NLST | Tobacco Use Supplement |
|---------------------|-------|------------------------|
| Male % | 59.0% | 58.5% |
| Age group | | |
| 55-59 yr. | 42.8% | 35.2% |
| 60-64 yr. | 30.6% | 29.3% |
| 65-69 yr. | 17.8% | 20.8% |
| 70-74 yr. | 8.8% | 14.7% |
| Black % | 4.4% | 5.5% |
| Hispanic Latino % | 1.7% | 2.4% |
| Current smoker | 48.2% | 57.1% |
| Median pack years | 48.0 | 47.0 |

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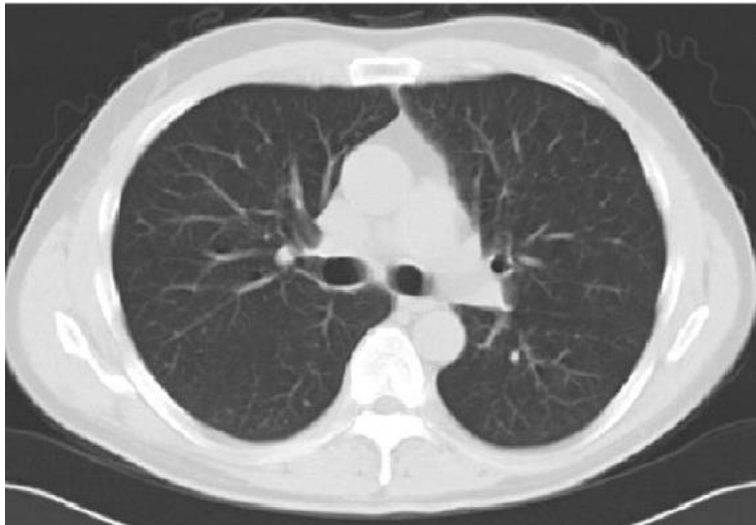
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- NLST initiated target enrollment plan after trial launch
 - 7 ACRIN sites based on accrual performance | regional demographics | resources
 - Worked with ACS, NCI Office of Communications, NMA
 - Costs of individual strategies varied from \$146-749/enrollee
 - Target sites: 9.3% to 15.2% ($p < 0.0001$) vs. Non-target sites: 3.5% to 3.8% ($p = 0.46$)
 - Across ACRIN: 8.4% minority participants | 7 Sites accounted for 77.6% of minorities

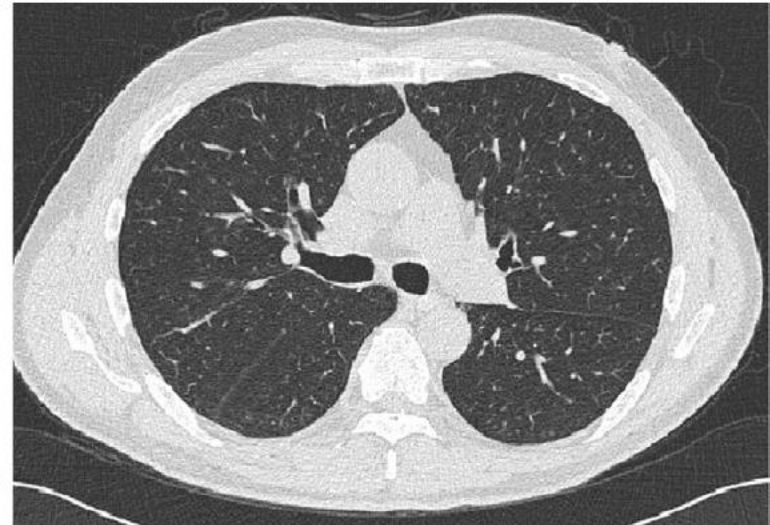


- Start early
- Sustainable plan

- Detection task: Detect & follow *changes* in nodules of ≥ 4 mm diameter
- “Low dose” | Balance spatial resolution & noise
- Radiologist panel reviewed various images from various acquisitions
- CT physicist team individually calibrated each of 16 scanner platforms



Thick section | smooth kernel

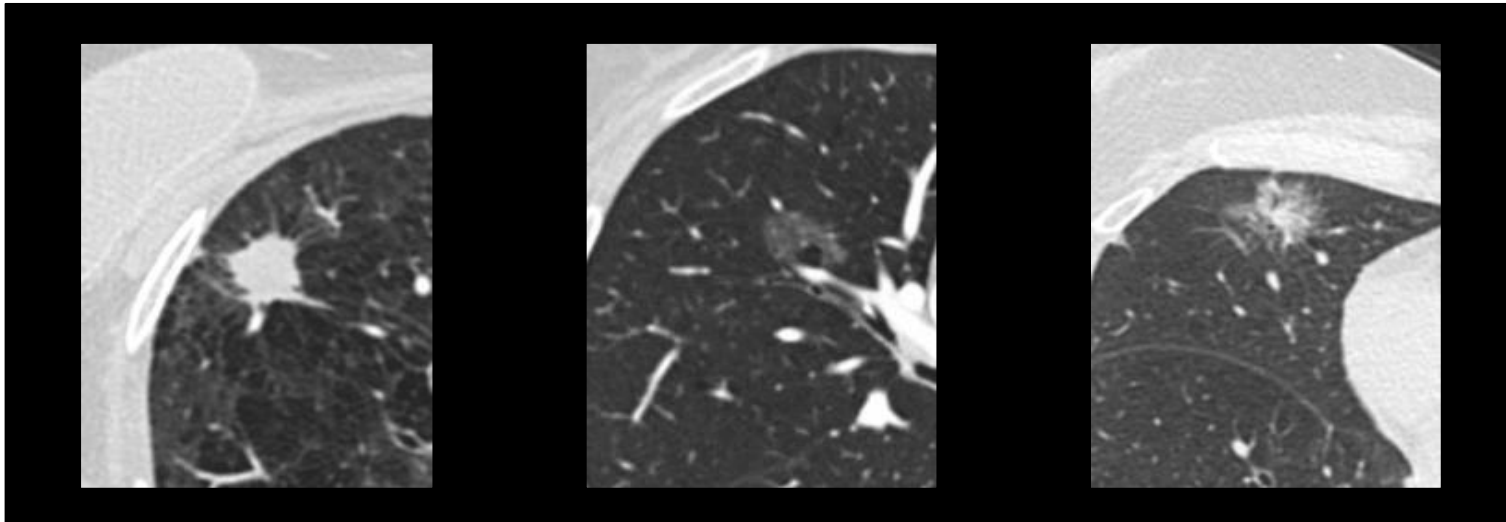


Thin section | sharp kernel

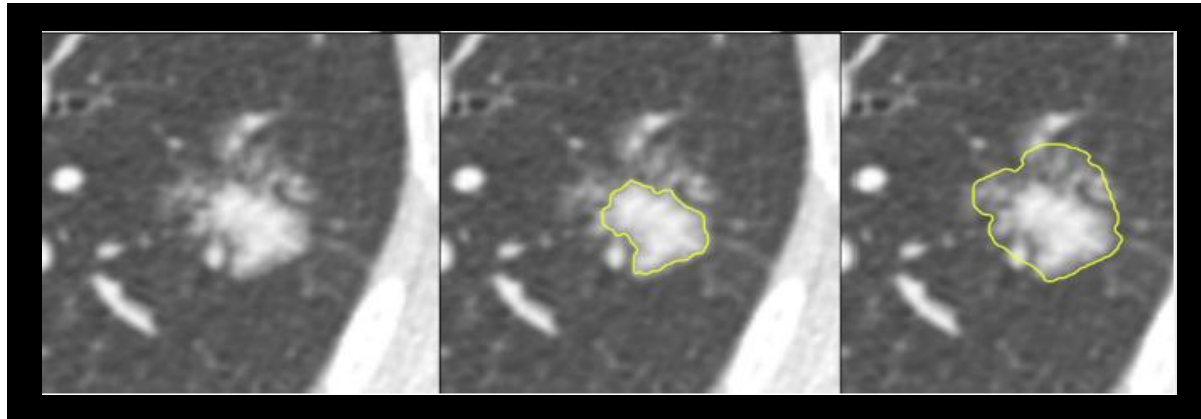


- Image acquisition & reconstruction are critical to characterization
- Two methods of nodule characterization
 - Semantic (visual): Agnostic to technique | low reader agreement
 - Quantitative features: Reproducible | sensitive to acquisition

- Nodule classification: Size, location, consistency, margins, evolution
- To calibrate readers: Training module (image quality & nodule types)
- In retrospective analyses reader agreement was moderate (N = 9)
 - Nodule growth: K coefficient = 0.55 (0.52 - 0.58)
 - Change in attenuation: K coefficient = 0.31 (0.27 - 0.52)
 - High level FU (Actionable change): K coefficient = 0.66 (0.63 – 0.69)



- Volumetry & mass (segmentation & feature extraction)
- NELSON used VDT to determine screen result in solid nodules
 - Feature analysis by nodule consistency
 - Solid: Volumetry (~ 90%) | Reproducible & accurate | $VDT \leq 400$ days → suspicious
 - Subsolid: SW only recently been developed for nodule segmentation
 - Subsolid: Volume & VDT | mass & MDT [where $MDT = \Delta t \times (\ln(2))/\ln(M2/M1)$]
 - Pairwise comparisons of CAD vs. Expert: K coefficient 0.54-0.72



Gietema HA. Radiology 2006; 24:251-257.
Colins J. Invest Radiol 2015; 50:168-173.
Scholten ET. Eur Respir J 2015; 45:765-773.



- Nodule features are important in classifying benign vs. malignant
 - Semantic | Computational | Some combination
- Semantic features are relatively insensitive to technique but have only moderate inter-reader agreement
 - Illustrated lexicons will be critical to “calibrating” across centers
- Computer vision features are sensitive to acquisition & reconstruction
 - Reduce variance
 - Measure reproducibility & accuracy across heterogeneous datasets



- Baseline risk of lung cancer: Eligibility, smoking, health status
- Screen results: [-] | [+] short term FU | [+] definitive FU
- Follow-up tests & results
 - Types of diagnostic testing performed: Histology | stage
 - Treatment approaches & complications
 - Outcomes: Lung cancer and all-cause mortality
 - Deaths: Lung cancer | management-related | other
- Other:
 - Medical resource utilization and costs
 - Tissue acquisition: Tumor | ACRIN (blood, sputum, urine)



■ NLST experience

- Vital status known for 97% of CT arm | 96% of CXR arm
- Diagnosis | Treatment completed at *non-NLST* sites
- LTF: Relocation | Lack of contact information

■ Alternatives to direct participant contact

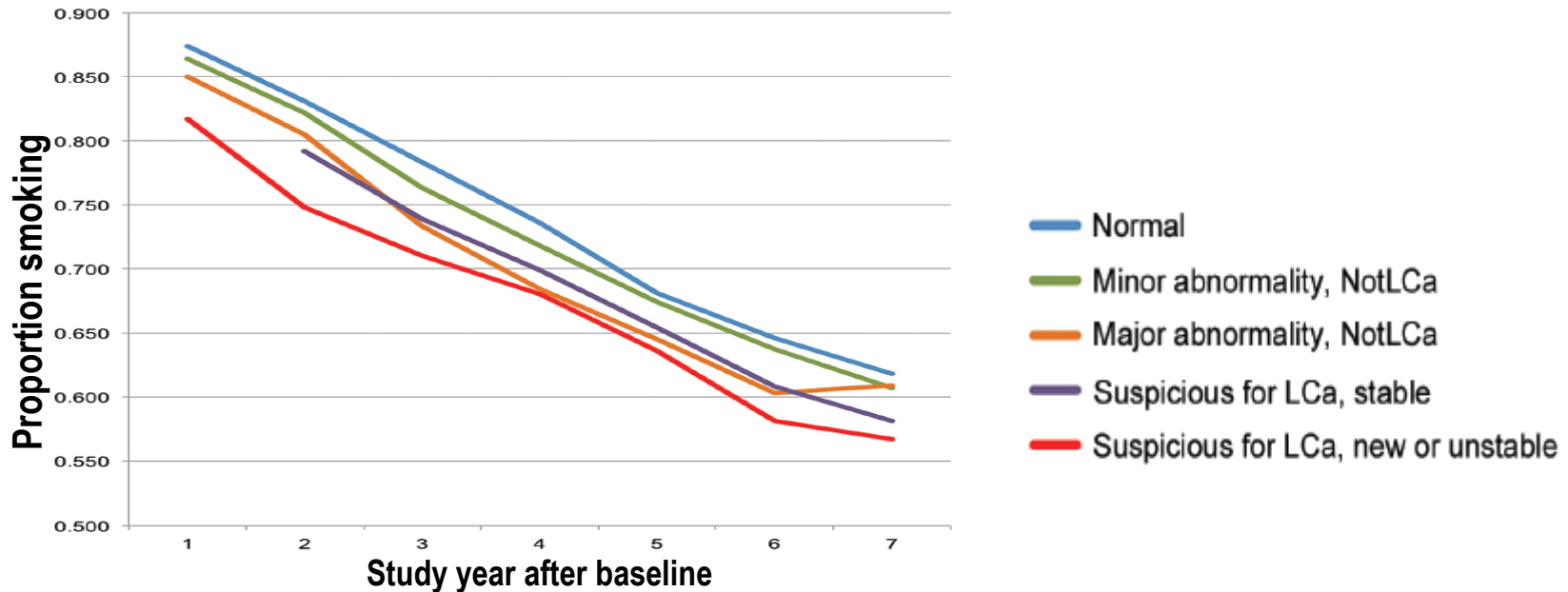
- Google searches
- Other personal contacts
- National Death Index

Must have reliable staff to maintain contact & track patients

Screening result and smoking cessation

- Variable evidence on screening as motivational tension
- Smoking cessation is significantly associated with positive screen

| Screening Result | Odds Ratio (95% CI) | P-value |
|--|------------------------|---------|
| Normal | Referent group | |
| Positive screen Stable from previous | 0.785 (0.706 to 0.872) | < 0.001 |
| Positive screen New or changed | 0.663 (0.607 to 0.724) | < 0.001 |





- 5As: Ask, Advise, Assess, Assist and Arrange (FU)]
- Examined PCP 5As practices and smoking cessation rates post-screen
- Frequency of PCP interventions:
 - 77.2% ask | 75.6% advise | 63.4% assess | 56.4% assist | 10.4% arrange
- Less intensive interventions were not associated with increased quit rates
- OR for *assist* = 1.40 (1.21-1.63) | for *arrange* = 1.46 (1.19 – 1.79)



- Ensure screen eligibility
- Adequate representation of at-risk minorities
 - Plan *early* for targeting special populations
 - Establish more robust mechanisms *within* communities of interest
- Standardized acquisition: low dose & enable computer vision
- Interpretation: Standardize terminologies using *illustrated lexicons*
- Longitudinal follow-up: *Dedicated program staff & tracking SW*
- Incorporate smoking cessation into *screening program*



Thanks!



- **Screening and treatment locations**
 - NLST sites performed screening
 - *Other* facilities completed diagnosis and/or treatment
- **Lost to FU**
 - Vital status known for 97% of CT arm | 96% of CXR arm
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These challenges hamper documentation of screening benefit



| NLST CT Technique Chart | Siemens 64 Sensation | GE – VCT (64) | Toshiba Aquilion | Philips MX8000 16 slice |
|--|----------------------|-----------------|------------------|-------------------------|
| kV | 120 | 120 | 120 | 120 |
| Gantry rotation time | 0.50 sec | 0.50 sec | 0.50 sec | 0.5 sec |
| mA (Regular – Large patient values) | 50-100 | 50-100 | 80-160 | 75-150 |
| mAs (Reg – Lg) | 25-50 | 25-50 | 40-80 | 37.5-75 |
| Scanner effective mAs (Reg – Lg) | 25-50 | 27-53 | 26.7-53.3 | 25-50 |
| Detector collimation (mm) - T | 0.6 mm | 0.625 | 2 mm | .75 mm |
| Number of active channels - N | 32 | 64 | 16 | 16 |
| Detector configuration – N · T | 32 x 0.6 mm | 64 x 0.625 | 16 x 2 mm | 16 x .75 mm |
| Collimation (operator console) | 64 x 0.6 mm | .625/.984/39.37 | NA | NA |
| Table incrementation (mm/rotation) - I | 19.2 mm | 39.37 mm | 48 mm | 18 mm |
| Pitch ([mm/rotation]/ beam collimation – I/NT) | 1.0 | 0.984 | 1.5 | 1.5 |
| Table speed (mm/second) | 38.4 mm/sec | 78.74 mm/sec | 96 mm/sec | 36 mm/sec |
| Scan time (40 mm thorax) | 11 sec | 5.1 sec | 4.2 sec | 11 sec |
| Nominal reconstructed slice width | 2 mm | 2.5 mm | 2 mm | 2 mm |
| Reconstruction interval | 1.8 mm | 2.0 mm | 1.8 mm | 1.8 mm |
| Reconstruction algorithm | B30 | STD | FC 10 | B or C |
| # Images/data set (40 cm thorax) | 223 | 200 | 223 | 223 |
| CTDI vol (Dose in mGy) | 1.9 – 3.8 mGy | 2.2 – 4.4 mGy | 2.7 – 5.4 mGy | 1.9 – 3.8 mGy |

 = Modifiable parameters on technologist console



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