Screening Programs
background and clinical implementation

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disclosures

I have no disclosures.

I have no conflicts of interest relevant to this talk.

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Overview

- Review the basis for decisions by USPSTF and CMS
- Implementation strategies & requirements
- Ongoing challenges—what we don't know

Major observations from the NLST

- Significant relative mortality reductions with CT screening
  - 20% decrease in lung cancer-specific mortality
  - 6.7% decrease in all-cause mortality
- "Positive" screen was defined as nodule ≥ 4 mm
- 24% CT screens were positive
- PPV of positive screen ~ 4% (maximally 5.2% at 3rd screen)
- Among those with false [+] screens complication rate < 0.1%
- NNS to prevent 1 death: 320
- Overdiagnosis estimated at 10-20%

NLST Investigators. NEJM 2011; 365(5):395-409

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timeline of events

08/2011 **NLST primary results published**

12/2013 **USPSTF Grade B recommendations**
Private insurers must cover CT screening
in those satisfying eligibility criteria

04/2014 **MEDCAC gives vote of low confidence**
Generalizability to Medicare population
Eligibility | Diagnostic creep
Costs
Harms: Repeat exams, complications, surgical mortality

01/2015 **ACA: Insurance will cover CT lung cancer screening**

02/2015 **CMS final decision to cover screening**

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Components of CMS coverage decision

- Beneficiary eligibility must be met
- Written order for LDCT screening during a screening counseling & shared decision making visit
  - Benefits and harms of screening
  - Importance of adherence to annual screening
  - Importance of smoking cessation/continued abstinence
  - Patient is asymptomatic
- Radiologist | Equipment | Site certification
- Submit data to national registry

Satisfaction of all of the above are required for reimbursement

http://www.acr.org/Quality-Safety/Lung-Cancer-Screening-Center

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The major challenges with implementation

- Ensuring quality across screening programs
  - Documenting satisfaction of CMS requirements
  - CT low exposure techniques
  - Standardized interpretation | management
  - Tracking and follow-up
- Defining the appropriate population to screen
- Reducing false positivity rates
- Diffusion across all socioeconomic groups
- Maintaining costs

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Who should be screened?

- Screen eligibility in US based on NLST
  - Designed for a clinical trial
  - Were NOT intended to inform optimal risk
- Can we do better?

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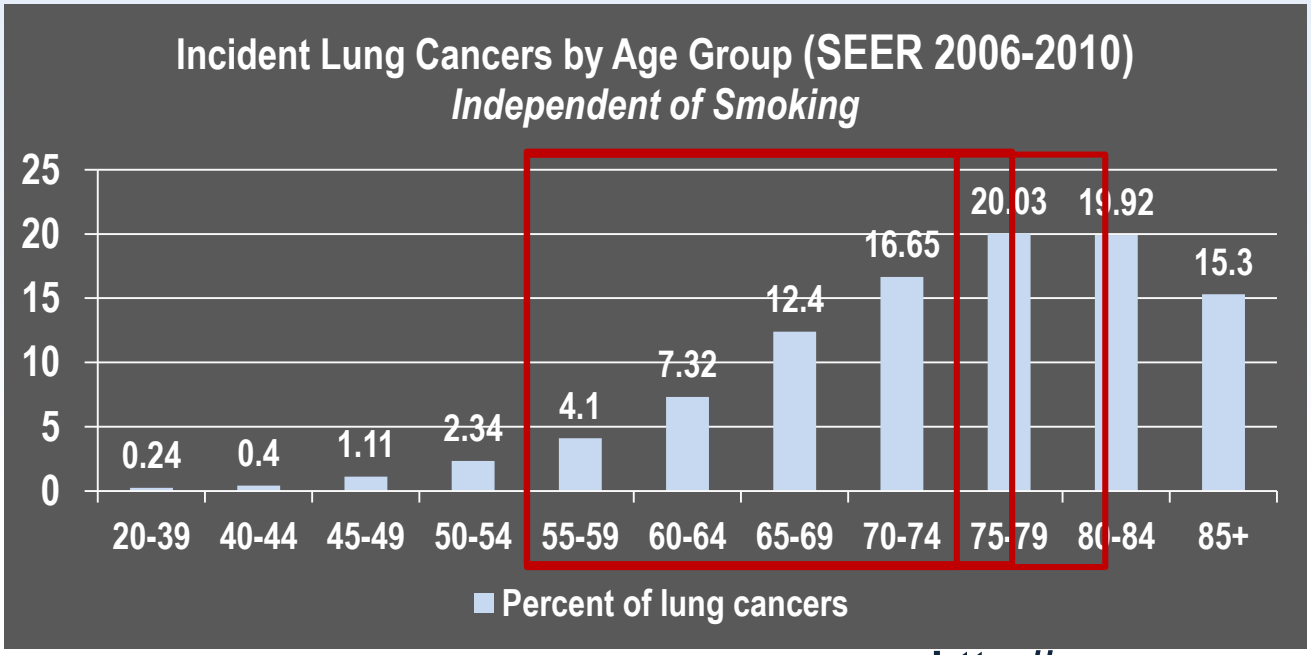
Proportion of lung cancer cases in US that satisfy NLST criteria

NLST Age 55-74 | current or former smoker
≥ 30 pack yrs | quit within 15 yrs.
< 30% of those diagnosed annually with lung cancer in US



http://seer.cancer.gov/

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Eligibility criteria

Criterion	NLST	USPSTF	CMS
Age	55-74 years	55-80 years	55-77 years
Smoking status	Current & Former	Current & Former	Current & Former
Smoking intensity	≥ 30 PKYs	≥ 30 PKYs	≥ 30 PKYs
Years quit	≤ 15 years	≤ 15 years	≤ 15 years
Symptoms	Absent	Absent	Absent

- NLST criteria account for < 30% of lung cancer cases in US
- Over time, the number of qualifying individuals will drop
- Increasing upper age threshold minimally increases the eligible pool

Moyer VA. Ann Intern Med 2014; 160:330-338.
Lung Cancer Screening, V 1.2015 J Natl Compr Canc Netw 2015; 13:23-34.
http://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2015-Press-releases-items/2015-02-05.html

Proposed eligibility criteria across organizations

Criterion	NLST / NCCN 1	USPSTF	CMS	NCCN Category 2
Age	55-74 years	55-80 years	55-77 years	
Smoking status	Current & Former	Current & Former	Current & Former	
Smoking intensity	≥ 30 PKYs	≥ 30 PKYs	≥ 30 PKYs	
Years quit	≤ 15 years	≤ 15 years	≤ 15 years	
Symptoms	Absent	Absent	Absent	
Additional Risks	NA	NA	NA	

Moyer VA. Ann Intern Med 2014; 160:330-338.
Lung Cancer Screening, V 1.2015 J Natl Compr Canc Netw 2015; 13:23-34.

Proposed eligibility criteria across organizations

Criterion	NLST / NCCN 1	USPSTF	CMS	NCCN Category 2
Age	55-74 years	55-80 years	55-77 years	≥ 50 years
Smoking status	Current & Former	Current & Former	Current & Former	Current & Former
Smoking intensity	≥ 30 PKYs	≥ 30 PKYs	≥ 30 PKYs	≥ 20 PKYs
Years quit	≤ 15 years	≤ 15 years	≤ 15 years	No maximum quit time
Symptoms	Absent	Absent	Absent	Absent
Additional Risks	NA	NA	NA	At least 1 additional risk factor ▪ Radon exposure ▪ Exposure to carcinogen ▪ FH lung cancer ▪ COPD, IPF ▪ Cancer history: • Lung | H&N • Lymphoma • Other tobacco-related

Moyer VA. Ann Intern Med 2014; 160:330-338.
Lung Cancer Screening, V 1.2015 J Natl Compr Canc Netw 2015; 13:23-34.

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Lahey Clinic experience with NCCN risk profiles

- Screening initiated 2012 (No cost)
- Eligibility: NCCN Category 1 and 2
- > 2300 patients screened (LTF: 25%)
- Annualized rates of lung cancer
  - 25% patients in Category 1 = 1.6%
  - 75% patients in Category 2 = 1.8%
- Take home: Additional lives could be saved by rationally expanding eligibility criteria

McKee BJ, et al. J Am Coll Radiol 2014; http://dx.doi.org/10.1016/j.jacr.2014.08.002

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Can mathematical models improve on risk profiling?

- Rule-based algorithms
  - Are easy to implement
  - Currently factor *few* known risk variables
  - Often *dichotomize* risk variables
- Can we rationally expand eligibility using models?
  - Factor *additional* known risk factors
  - Exploit full information content of continuous variables
  - Consider non-linear effects of some variables

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Using risk models to define screening cohorts

PLCO2012 Logistic-Regression Model of 6-Yr Risk Lung Cancer Diagnosis

Variable	Odds Ratio (95% CI)	P Value
Age, per 1-yr increase	1.081 (1.057-1.105)	< 0.001
Race | Ethnic group		
White	1.000	Reference
African American	1.484 (1.083 - 2.033)	0.01
Hispanic	0.475 (0.195 - 1.160)	0.10
Asian	0.627 (0.332 - 1.185)	0.15
American Indian or Alaskan Native	1	
Native Hawaiian or Pacific Islander	2.793 (0.992 - 7.862)	0.05
Education, per increase of 1 level	0.922 (0.874 - 0.972)	0.003
Body mass index, per 1-unit increase	0.973 (0.955 – 0.991)	0.003
COPD (Yes. vs. No)	1.427 (1.162 – 1.751)	0.001
Personal history of cancer (Yes vs. No)	1.582 (1.172 – 2.128)	0.003
Family history of lung cancer (Yes vs. No)	1.799 (1.471 – 2.200)	< 0.001
Smoking Variables		
Smoking status (Current vs. Former)	1.297 (1.047 – 1.605)	0.02
Smoking intensity		
Duration of smoking, per 1-yr increase	1.032 (1.014 – 1.051)	0.001
Smoking quit time, per 1-yr increase	0.970 (0.950 – 0.990)	0.003

- AUC = 0.803 — Development dataset: 36,286 PLCO control group smokers
- AUC = 0.797 — Internal validation: 37,332 PLCO invention group smokers
- AUC = 0.701 — External validation: 51,033 NLST participants

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Overall findings

- At $PLCO_{2012}$ risk ≥ 0.0151, death rate in NLST CT arm is consistently lower than in CXR arm
- NNS to prevent 1 cancer death = 255
- $PLCO_{2012}$ vs. USPSTF criteria (PLCO intervention smokers)
  - 8.8% fewer screenees with $PLCO_{2012}$ than USPSTF
  - 12.4% more cancers using $PLCO_{2012}$

Tammemagi MC et al. PLoS Med 11(12): e1001764. doi:10.1371/journal.pmed.1001764

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How do we reduce false positive screens?

- NLST defined “positive” screen as nodule ≥ 4 mm
- What does analysis of the NLST data show us?

NLST Positive CT Screens

Impact of nodule size & screening time point on predictive value

Size	T0 Screen		T1 Screen		T2 Screen	
	# nodules	# LC (PPV)	# nodules	# LC (PPV)	# nodules	# LC (PPV)
TOTAL*	7040 (100.0%)	267 (3.8%)	6785 (100.0%)	161 (2.4%)	3914 (100.0%)	203 (5.2%)
4-6 mm	3668 (51.0%)	18 (0.5%)	3822 (56.3%)	12 (0.3%)	2023 (51.7%)	15 (0.7%)
7-10 mm	2115 (30.0%)	35 (1.7%)	1959 (28.9%)	46 (2.4%)	1131 (28.9%)	58 (5.1%)
11-20 mm	932 (13.2%)	111 (11.9%)	815 (12.0%)	74 (9.1%)	588 (15.0%)	86 (14.6%)
21-30 mm	195 (2.8%)	58 (29.7%)	114 (1.7%)	20 (17.5%)	100 (1.5%)	23 (23.0%)
> 30 mm	109 (1.5%)	45 (41.3%)	55 (0.8%)	8 (14.5%)	62 (1.6%)	20 (32.8%)
Unknown	21 (0.3%)	0	20 (0.3%)	1 (0.6%)	10 (0.3%)	1 (10%)

* Numbers relate only to lung cancers observed with positive screens.

The minimum threshold for positive screens can be increased

NLST Research Team. NEJM 2011; 365:395-409.
NLST Research Team. NEJM 2013; 368:1980-1991.
Aberle DR et al. NEJM 2013; 369:920-931.

ACR LUNGRads™ Version 1.0

	Grade	Baseline	Management	Probability Lung cancer	Population Prevalence
INCOMPLETE	0	Prior chest CT exam(s) being located for comparison Part or all of lungs cannot be evaluated	Add'l screening CT and/or prior chest CT exams	NA	1%
NEGATIVE	1	NO lung nodules	Annual Screening in 12 months	< 1%	90%
		BENIGN Nodule(s): Contain fat or calcification			
Benign Appearing	2	SOLID < 6 mm PSN < 6 mm total diameter GGN < 20 mm			
Probably Benign	3	SOLID ≥ 6 to < 8 mm at baseline PSN ≥ 6 mm total diameter; solid part < 6 mm GGN ≥ 20 mm	6 month LDCT, then Annual Screening	1-2%	5%
SUSPICIOUS	4A	SOLID ≥ 8 mm to < 15 mm PSN: ≥ 6 mm total, solid part ≥ 6 mm to < 8 mm Endobronchial nodule	3 month LDCT (PET-CT if ≥ 8 mm solid)	5-15%	2%
	4B	SOLID ≥ 15 mm PSN Solid component ≥ 8 mm	Chest CT or PET-CT, Tissue sampling depending on probability of malignancy and comorbidities.	> 15%	2%
	4X	OTHER Category 3 or 4 nodule with additional suspicion			
OTHER	S	▪ Significant or potentially significant findings unrelated to lung cancer ▪ May add on to Category 0-4 codes	As appropriate to the findings	NA	10%

NOTE: A modifier "C" is added to Categories 0-4 for patients with prior lung cancer returning for surveillance screening.

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Lahey Clinic experience with LungRADS 1.0 interpretation criteria

Results (N = 2180)	NCCN / NLST	LungRADS
Interpretation Category		
Negative (LungRADS 1 & 2)	1579 (72.4%)	1949 (89.4%)
Positive (LungRADS 3 & 4)	601 (27.6%)	231 (10.6%)
Suspicious (LungRADS 4)	93 (4.3%)	93 (4.3%)
Outcomes in 1603 (74%) with FU > 12 months		
PPV (clinical and histologic)	6.9%	17.3%
PPV (histologic only)	6.2%	15.5%
Lung cancer diagnoses	29 (1.8%)	29 (1.8%)

NOTE: 3 diagnoses of lung cancer based on imaging & multidisciplinary consensus.

- LungRADS implementation increased PPV of [+] screen to 17.3%
- Of 152 patients with > 12 months FU: no increase in false [-] results

McKee BJ, et al. J Am Coll Radiol 2014; http://dx.doi.org/10.1016/j.jacr.2014.08.004

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Diagnostic models vs. rule-based algorithms for indeterminate nodules

What about using mathematical models for diagnostic prediction?

- Include additional variables associated with lung cancer
- Exploit information content of continuous variables
- Exploit visual (semantic) features
  - Size and consistency
  - Anatomic location
  - Margin characteristics
  - # nodules observed
- Quantitative features (another day…)

The McWilliams model

Predictor Variables	Parsimonious Model		Full Logistic Regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (Centered at 62; per year)			1.03 (0.99-1.07)	0.16
Sex (Female vs. Male)	1.91 (1.19-3.07)	0.008	1.82 (1.12-2.97)	0.02
FH (Yes vs. No)			1.34 (0.83-2.17)	0.23
Emphysema (Yes vs. No)			1.34 (0.78-2.33)	0.29
Nodule size (Centered at 4 mm)	Non-linear	< 0.001		< 0.001
Nodule consistency: GGN			0.88 (0.48-1.62)	0.68
PSN			1.46 (0.74-2.88)	0.28
Solid			Reference	
Lobe: Upper vs. other	1.82 (1.12-2.98)	0.02	1.93 (1.14-3.27)	0.02
Nodule count per scan [1]			0.92 (0.85-1.00)	0.049
Spiculation (Yes vs. No)	2.54 (1.45-4.43)	0.001	2.17 (1.16-4.05)	0.02

[1] Nodule count centered at 4

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McWilliams diagnostic prediction models: performance

- 2 models
  - Parsimonious (all variables significant at $P < 0.05$)
  - Full (known variables significant at $P < 0.25$)
- Development dataset: PanCan | Validation: BCCA
- Truth: Histology or ≥ 2 yrs follow-up
- Performance: AUC

Model type		PanCan AUC (95% CI)	BCCA AUC (95% CI)
Parsimonious	All nodules	0.941 (0.911-0.962)	0.960 (0.927-0.980)
	Nodules ≤ 10 mm	0.894 (0.833-0.937)	0.907 (0.822-0.963)
Full	All nodules	0.942 (0.909-0.966)	0.970 (0.945-0.986)
	Nodules ≤ 10 mm	0.891 (0.825-0.942)	0.938 (0.872-0.978)

NOTE: Above models exclude spiculation as a variable.

McWilliams A et al. NEJM 2013;369:910-919.

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Summary

- Screening implementation must be standardized, involve data collection, FU, and QC
- Robust data management and tracking
- Opportunities for improvement
  - Risk profiling (who should we screen)
  - Diagnostic risk (what is the indeterminate nodule)
- Requirement: we collect the data necessary to inform those decisions

Thanks!