

Combining Biomarkers with Lung Cancer Low-Dose CT Screening - Assessing Potential Impact Via Simulation Modeling

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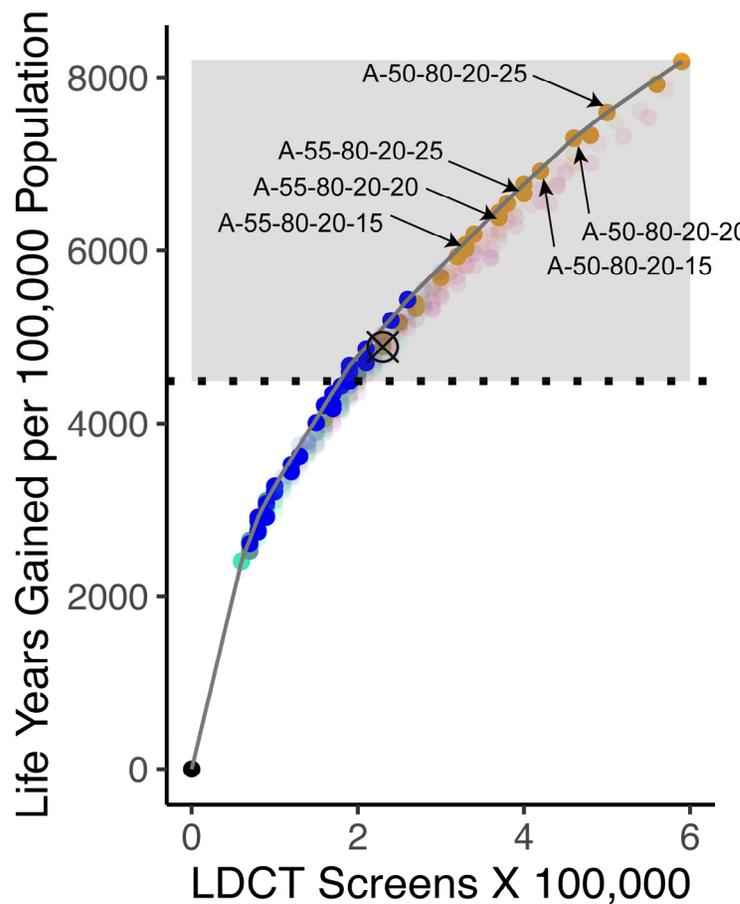
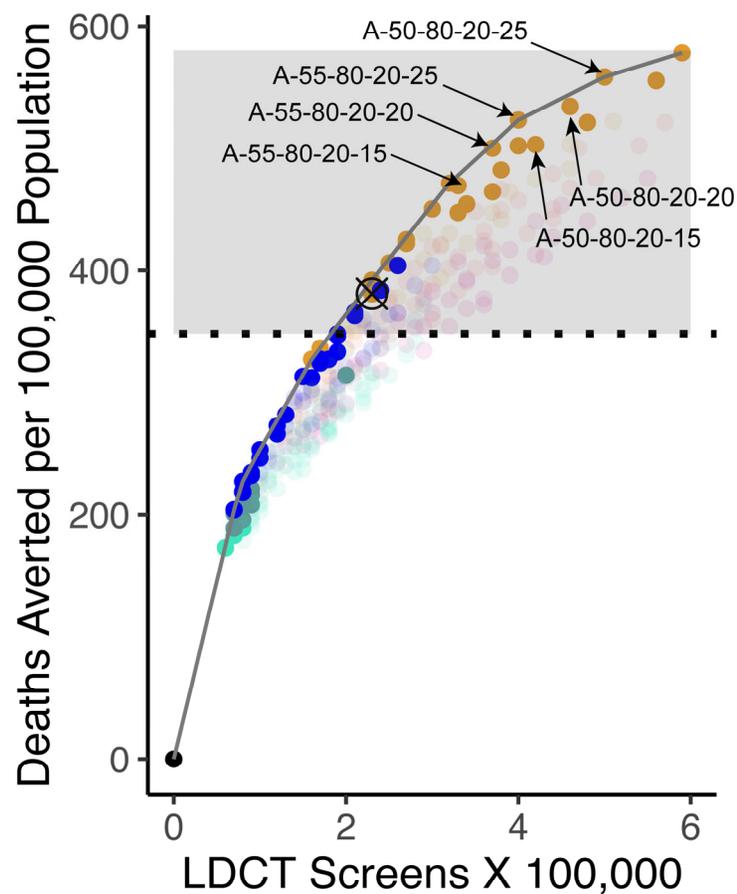
Outline

- Lung cancer screening
- Biomarkers and lung cancer screening
- Simulations of eligibility and population risk
- Conclusions

Lung Cancer Screening

- **Annual** low-dose CT for current and former smokers with at least **30 pack-years** of exposure and **no more than 15 years since quitting**
- Recommended by the USPSTF since 2014 – **ages 55-80**
 - **A-55-80-30-15**
- Recommended by CMS since 2015 – **ages 55-77**
 - Shared-decision making process
- New 2020 USPSTF draft recommendations (July 2020)
 - Reduce pack year criterion to **20 pack-years**
 - Reduce minimum age criterion to **age 50**
 - **A-50-80-20-15**

**Decision Analysis
For USPSTF**



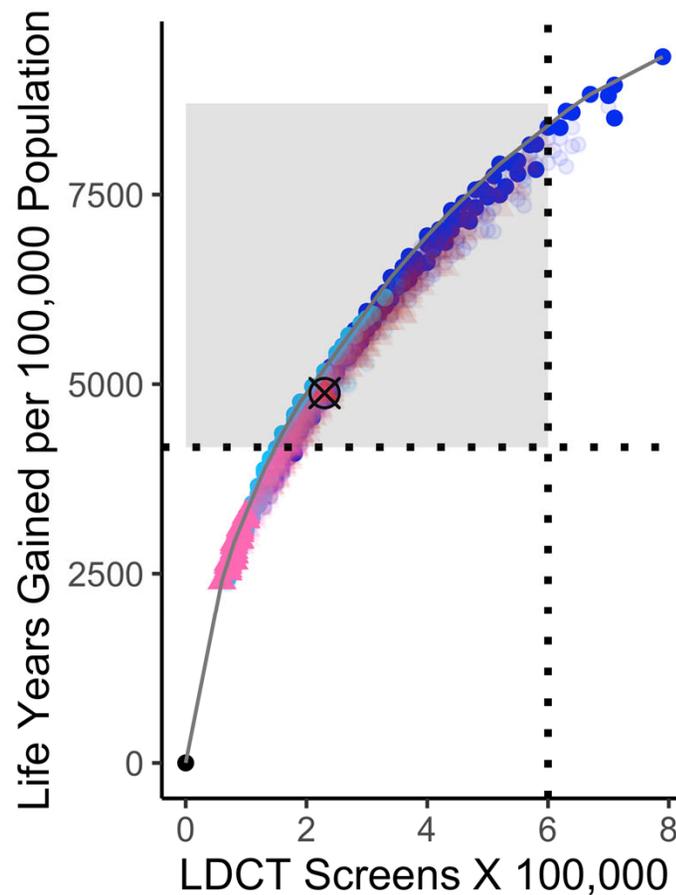
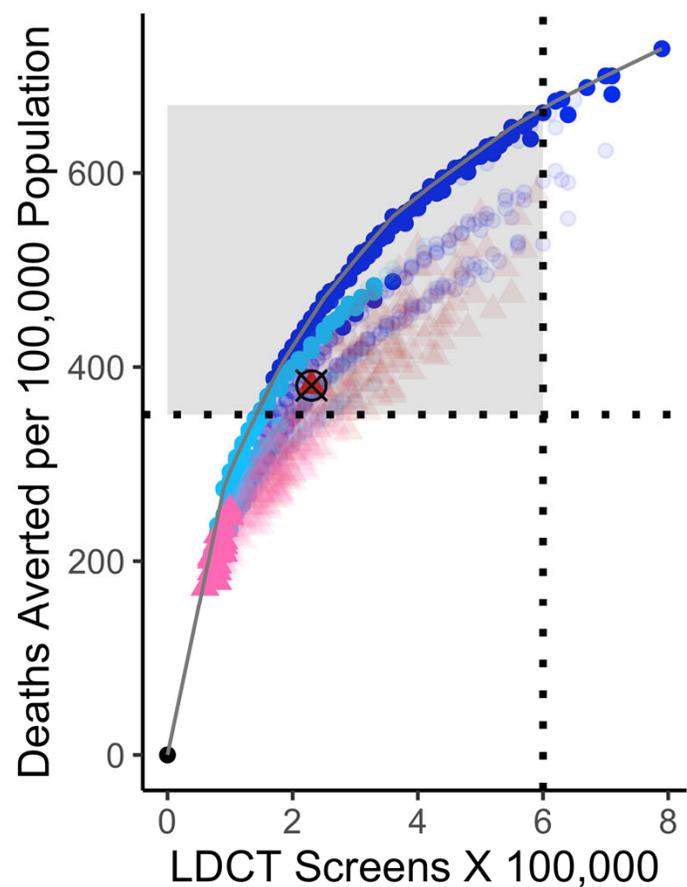
Freq-Stop Age

- A-75
- A-77
- A-80
- B-75
- B-77
- B-80
- No Screen
- ⊗ 2013 USPSTF

Lung cancer screening

- First cancer screening modality with eligibility depending on “risk”
- Not perfect, eligibility based on age and smoking exposure
- Other key lung cancer risk factors are ignored in major guidelines
 - Race/ethnicity, COPD, SES, family history, cancer history
 - Other guidelines do consider these independently or within a risk model
- Risk-based screening criteria proposed as an alternative
 - Based on multivariate risk models; e.g. PLCOm2012

**Decision Analysis
For USPSTF**



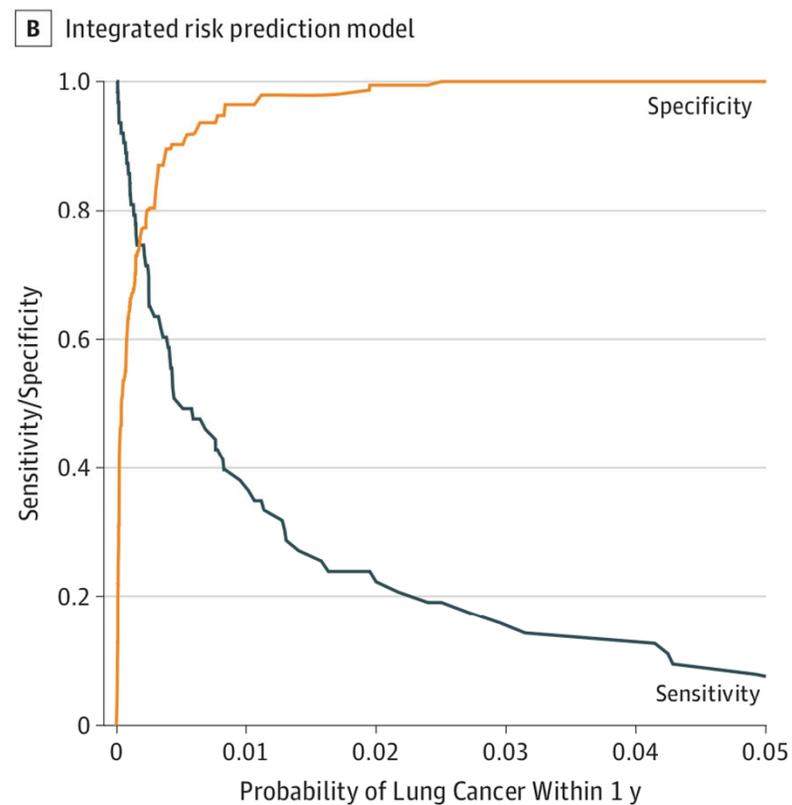
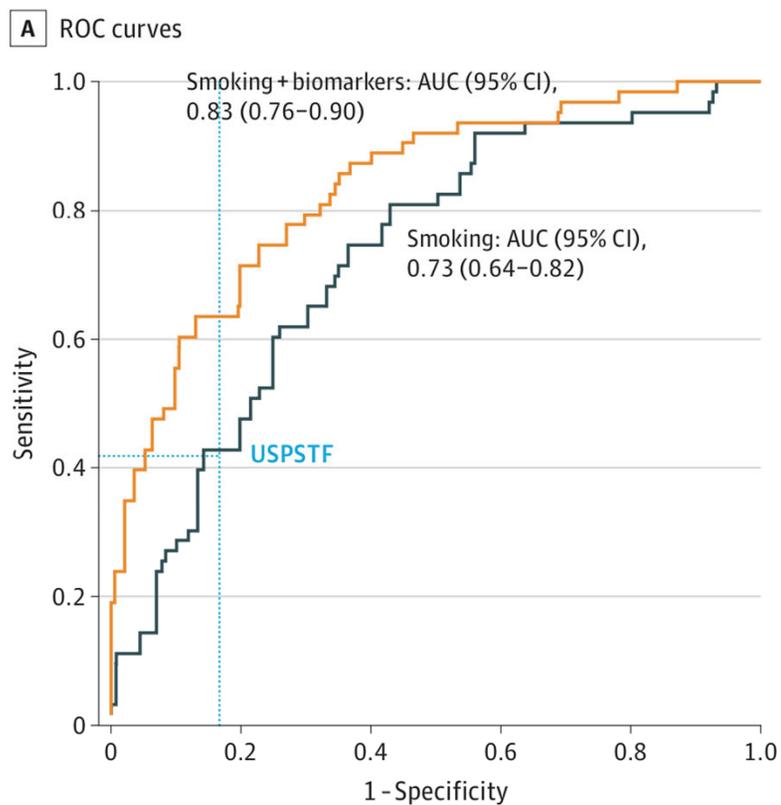
Freq-Eligibility

- A-risk model-based
- B-risk model-based
- ▲ A-risk factor-based
- ▲ B-risk factor-based
- No Screen
- ⊗ 2013 USPSTF

Biomarkers potential role under current screening recommendations

- Improve eligibility
 - Decide if someone **eligible** should proceed with LDCT screening or not – **Rule out**
 - Particularly those at the lower risk level among eligible
 - Decide if someone **not-eligible** should be screened – **Rule in**
 - Particularly those at the higher risk level among non-eligible
- Improve screening management and outcomes
 - Determine which nodules to follow-up
- Alternative to low-dose CT
 - Hard to reach populations
 - LMICs
 - Could trigger a low-dose or a regular CT

Figure 3. Receiver Operating Characteristic (ROC) Curve Analysis in the Validation Study (European Prospective Investigation Into Cancer and Nutrition [EPIC] and Northern Sweden Health and Disease Study [NSHDS], Ever Smokers)



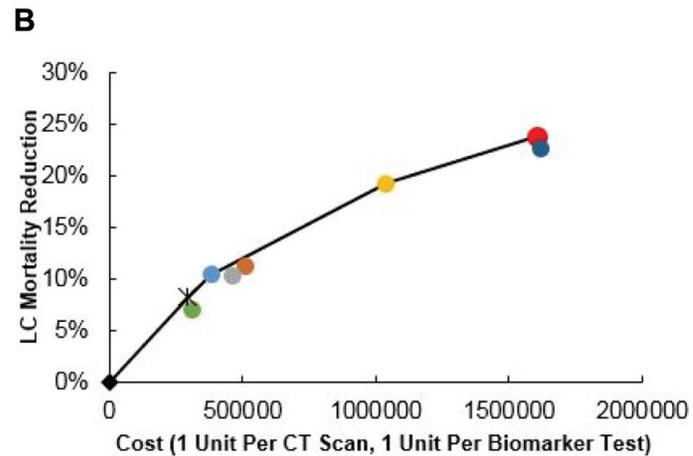
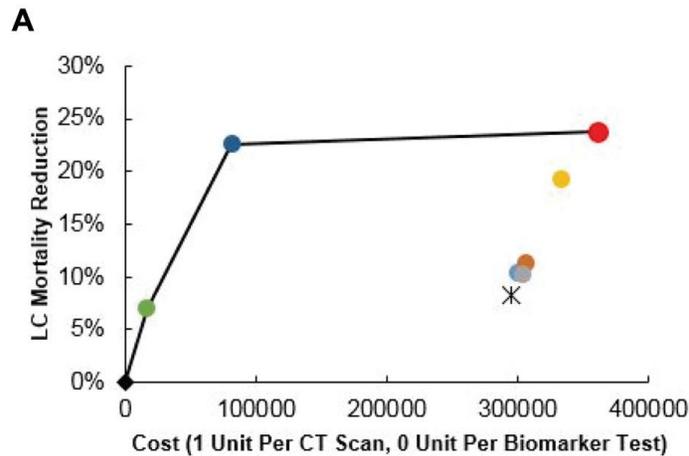
CISNET Lung Working Group

New funding period 2020-2025

- **Aim 2.3. Evaluate the potential benefits of putative genetic and other biomarkers that could be adopted to enhance the effectiveness of LDCT lung cancer screening**
 - Focus on *ready-for-prime-time* biomarkers
 - Inform models with real data; e.g., correlation between biomarker levels and risk, sens/spec

Past work

- Modeling of hypothetical biomarkers
 - Rule in criteria – Kong et al MDM Policy & Practice 2016
 - *Improving nodule follow-up* – Stanford Group, under review
- Ongoing collaboration with S. Hanash, Z. Feng & M. Tammemagi – PLCO U01



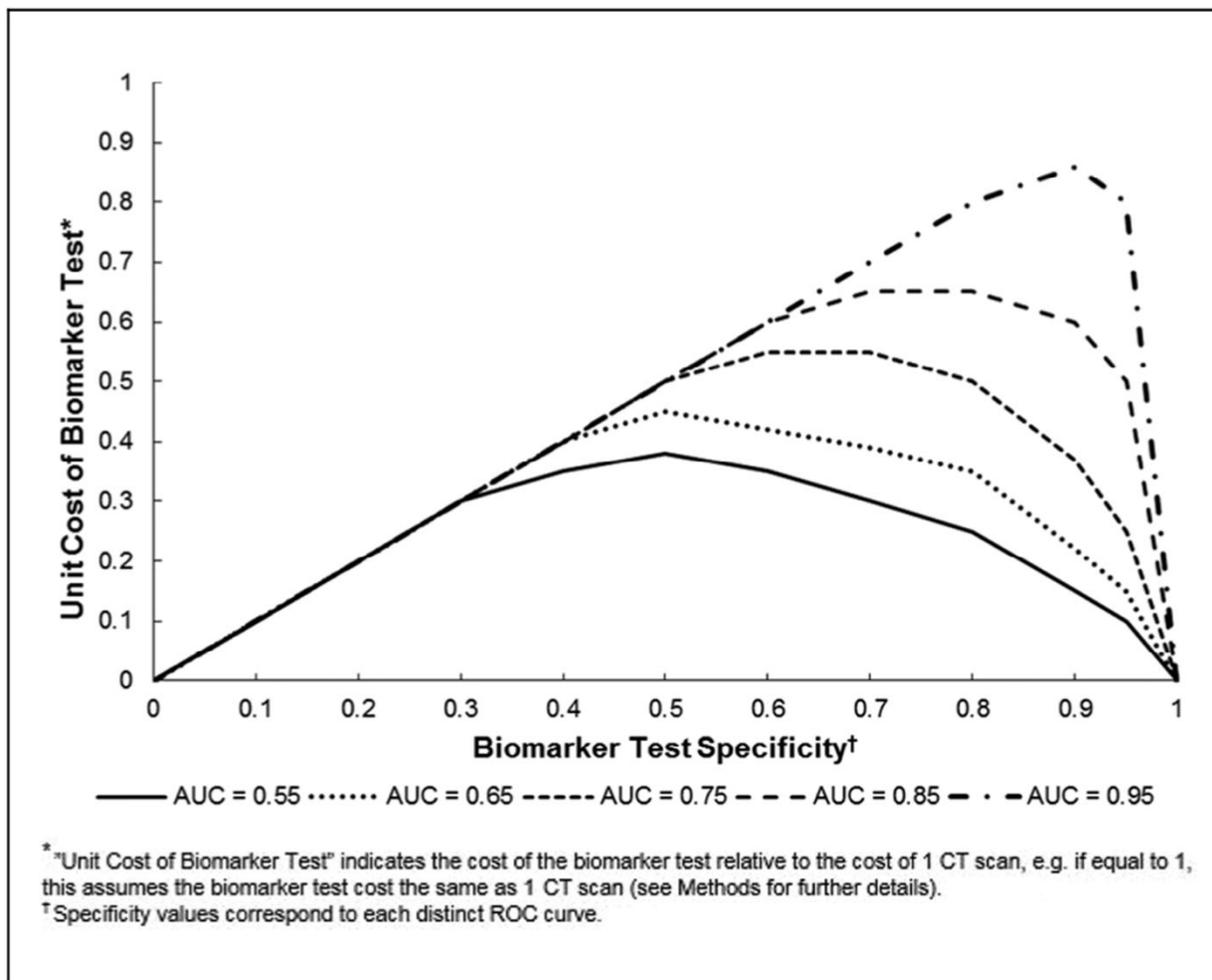
Biomarker
sensitivity = 0.75
specificity = 0.95

Cost
A – free
B – equal to CT

- Strategy 1 – CT screening for CMS-eligible; biomarker test[†] for years-since-quit-ineligible (i.e. >15 years)
- Strategy 2 – CT screening for CMS-eligible; biomarker test[†] for pack-year-ineligible (i.e. <30 pack-years)
- Strategy 3 – CT screening for CMS-eligible; biomarker test[†] for age-ineligible (i.e. ages ≥45 and <55)
- Strategy 4 – CT screening for CMS-eligible; biomarker test[†] for year-since-quit or pack-year ineligible
- Strategy 5 – CT screening for CMS-eligible; biomarker test[†] for all CMS-ineligible, ages ≥45 and ≤77
- Strategy 6 – Biomarker test[†] for all CMS-eligible
- Strategy 7 – Replace CMS eligibility criteria with biomarker test[†] for all, ages ≥45 and ≤77
- ✕ CT only (current standard)
- ◆ No screening
- Efficiency frontier

[†] If biomarker test results were positive, a screening CT was performed.

Efficiency cost thresholds as a function of biomarker specificity and AUC



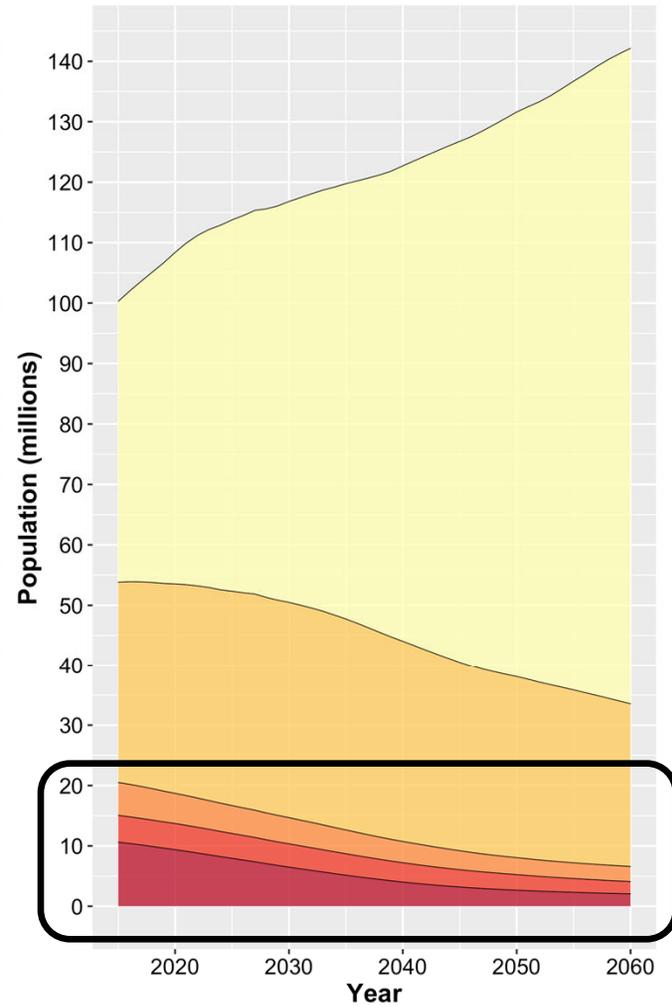
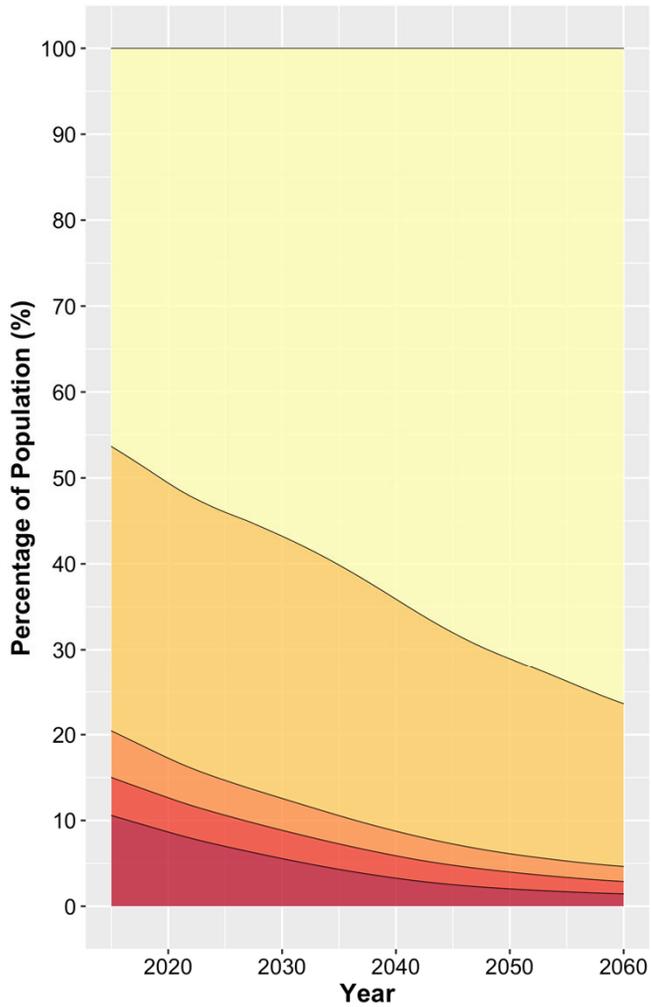
Biomarkers to **Rule in**

- Assuming draft USPSTF recommendations become final
 - **A-50-80-20-15** (20 pack years)
- What about ever smokers with **less than 20 PY** or **more than 15 years since quitting**?
- Never smokers should not be screened for lung cancer. Probably also true for low intensity smokers
- What about the 10-20 PY population?

What is the lung cancer burden among eligible and non-eligible?

Simulations to identify:

- Number of people in the 10-20 PY category who will never become eligible
- Number and percentage of lung cancers in this sub-population
- Potential impact of screening in this sub-population (deaths averted & LYG)



Percentage and number eligible will go down as smoking continues to decrease

Status

- Never smoker
- Not elig-PY10
- Elig-PY10 & Not elig-PY20
- Elig-PY20 & Not elig-PY30
- Elig-PY30

Simulations of the 1960 birth cohort

- US individuals born in 1960
- Consistent with Decision Analysis for the USPSTF
- Focus on impact on a given population cohort (rather than overall)
- Simulations using the University of Michigan CISNET model and the CISNET Smoking History Generator
 - Account for the projected smoking patterns for this cohort

Population by PY/eligibility

	Overall	Ever eligible under 20 PY criteria	Ever eligible under 20 PY but not 10 PY criteria
Number of individuals	100,000	23,875	7,170
Percentage	100%	23.9%	7.2%

Preliminary results, please don't cite

Lung Cancer Burden by PY/eligibility

	Overall	Ever eligible under 20 PY criteria	Ever eligible under 20 PY but not 10 PY criteria
Cases	4,967	3,287 66.2%*	361 9.9%*
Deaths	4,069	2,716 66.8%*	292 9.7%*

*percentage over total
Preliminary results, please don't cite

Screening impact under A-50-80-20-15

	Overall	Ever eligible under 20 PY criteria	Ever eligible under 20 PY but not 10 PY criteria
LC deaths averted	356 8.7%**	356 13.1%**	0
LYG	5488	5488	0

**Mortality reduction within group
Preliminary results, please don't cite

Screening impact under A-50-80-10-15

	Overall	Ever eligible under 20 PY criteria	Ever eligible under 20 PY but not 10 PY criteria
LC deaths averted	380 9.3%*	361 13.3%*	19 6.4%*
LYG	5986	5898	365

**Mortality reduction within group
Preliminary results, please don't cite

Caveats

- Preliminary results from a single CISNET model
- No explicit modeling yet of potential impact of using a biomarker to improve the selection of individuals
- Simulations assume screening under ideal conditions
 - Uptake/compliance

Conclusions

- Lots of room for improvement (a lot of cancers left untouched, screening sensitivity/specificity)
- An effective biomarker could:
 - Identify individuals who should be screened but do not meet eligibility criteria
 - Improve effectiveness on the eligible population
- Modeling can assist with:
 - Assessing the burden and potential benefit
 - Determining trade-offs between biomarkers sensitivity/specificity and costs
 - Identifying the populations who could benefit most from biomarker use given test characteristic and risk profiles
 - Assessing the potential for the joint use of biomarkers and risk prediction models

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