A Cluster Randomized Interventional Study of a Blood-Based Lung Cancer Screening Test in Primary Care Practices: The FIRSTLUNG Study, NCT06145750

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RATIONALE:

Lung cancer screening (LCS) remains underutilized in the United States, in spite of proven mortality benefit,[1,2] such that in 2022 only 18% of patients who were eligible received a Low Dose CT (LDCT) scan for LCS[3]. We postulated that if a peripheral blood test which was highly sensitive for lung cancer were available, and more convenient for patients than a CT scan, it might augment the rate of LCS. With this aim, DELFI Diagnostics developed a blood-based genomic lung cancer screening test (pWGFrag-Lung, FirstLook Lung)[4*] that could be obtained as a routine annual blood draw in a primary care setting. **Here we present results of a cluster randomized trial to determine whether the availability of the blood test increased lung screening rates.**

METHODS

Clinics:

Primary Care Practices across multiple US health systems were block randomized 1:1 to:

- Arm A = usual care (LDCT alone) or
- Arm B = usual care + access to the blood test

Patients eligible for analysis:

- Met 2021 USPSTF criteria for lung cancer screening,[5] and
- had never completed Lung Cancer Screening (LCS) or
- **were past due for their annual screening >15 months.**

Outcomes were compared using time-to-event analyses.

Multi-variable analyses adjusted for patient (age, sex, race/ethnicity, pack-year smoking history, current smoking status) and medical practice (network, rural/urban status) characteristics.

Patients were followed up to 11 months.

Outcomes:

1. **Primary Outcome** = completion of "any lung cancer screening" (LDCT or blood test)
2. **Secondary Outcome** = completion of LDCT.

RESULTS

28 primary care practices were randomized:

15 practices to usual care (Group A; 1662 eligible patients), and

13 practices to usual care plus access to the blood test (Group B; 1291 eligible patients).

Primary outcome: Any lung cancer screening (LDCT or blood test) occurred more frequently in Group B practices (20.9%) than Group A practices (8.4%): multi-variable HR = 2.73 (95% CI: 1.91, 3.89; p < 0.001).

Secondary outcome: LDCT screening was more common in Group B (13.4%) than Group A (8.4%): multi-variable HR: 1.47 (95% CI: 1.14, 1.89; p = < 0.01).

REFERENCES:

1: "Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening": The NLST Research Team. N Engl J Med 2011;365:395-409, VOL. 365 NO. 5

2: "Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial": Harry J. de Koning, M.D et. al., N Engl J Med 2020;382:503-513, VOL. 382 NO. 6

3: The American Lung Association's "State of Lung Cancer 2025"

4: "Clinical Validation of a Cell-Free DNA Fragmentome Assay for Augmentation of Lung Cancer Early Detection", Mazzone et al Cancer Discov. 2024 Jun 6;14(11):2224–2242.

5: USPSTF. JAMA. 2021;325(10):962-970.

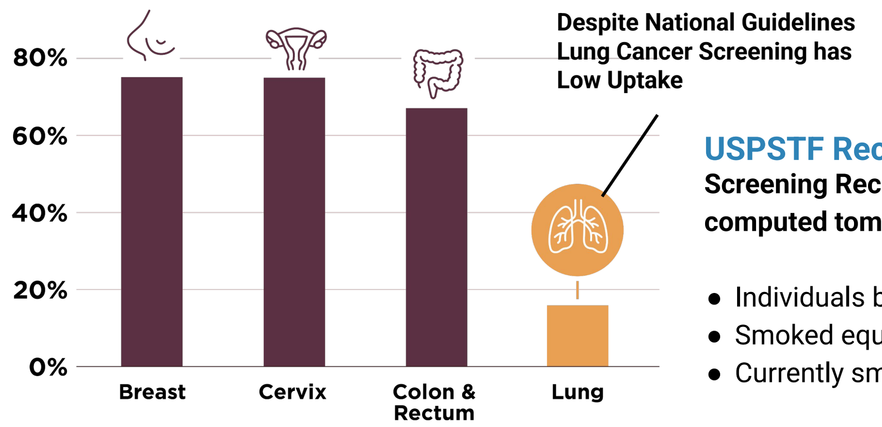
6: Presented at ATS 2026; Poster Board #608: "FIRSTLUNG L301: Baseline Socioeconomic Characteristics of a Cluster Randomized Clinical Utility Trial Evaluating Blood-Based Lung Cancer" Screening Across Diverse Communities.

7: Kazi MAI, Qureshi I, Sharma A, et al. From detection to delay: real-world gaps in post-Cologuard colonoscopy adherence. J Gastrointest Cancer. 2025;56(1). doi:10.1007/s12029-025-01350-5

***DISCLAIMER**

The FirstLook Lung test is a laboratory-developed test. This test was developed, and its performance characteristics were determined by DELFI Diagnostics. It has not been cleared or approved by the US Food and Drug Administration (FDA). The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests."

Figure 1:
USPSTF Recommend Cancer Screening and Association with Uptake



USPSTF Recommend

Screening Recommendations for lung cancer with low-dose computed tomography (LDCT) every year

- Individuals between the ages of **50 and 80 years old.**
- Smoked equivalent of average of **1 pack a day for 20 years**
- Currently smoke, or have quit within the past 15 years

Figure 2:
Performance of the Blood-based Test made Available in the Study

= pWGFrag-Lung (FirstLook Lung)[4]

For a blood-based lung cancer screening test, sensitivity is prioritized over specificity, as false-positive results are efficiently resolved through already well-defined LDCT pathways. Positive results enter the usual care LDCT screening pathway.

High Sensitivity and Negative Predictive Value of the blood-based test

Blood-based Cancer Screening Test Performance	
Screening-Population Sensitivity*[1]	80%
Screening-Population Specificity*	56%
NPV[1]	99.8%

*Test performance adjusted to the USPSTF eligible lung cancer screening population.

[2] Unpublished data on file DELFI Diagnostics Inc.

Figure 3:
Cluster Randomized Trial design of FIRSTLUNG

CME = Continuing Medical Education

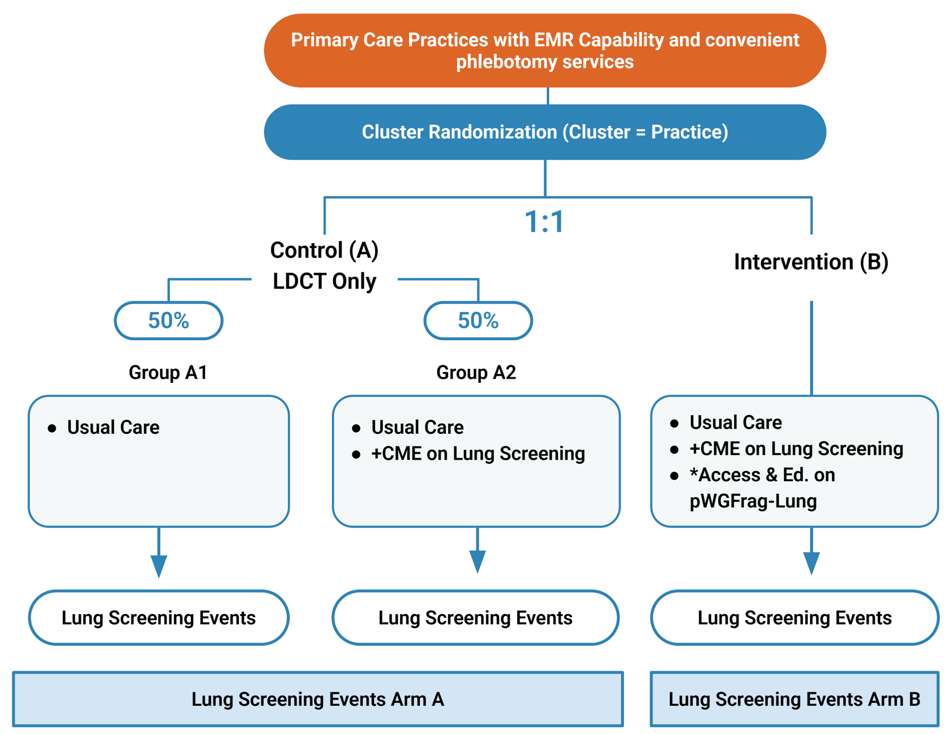
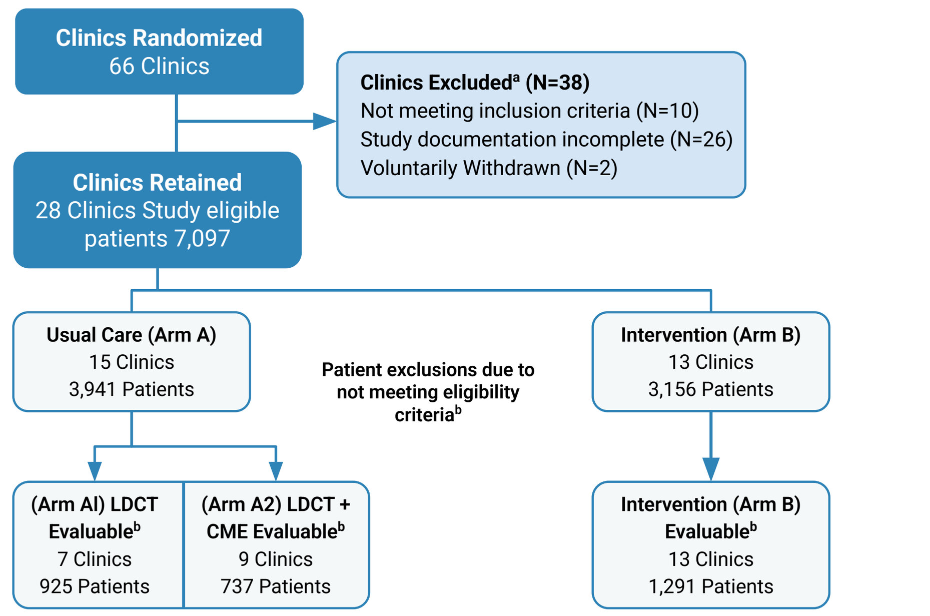


Figure 4:
Consort Diagram: Study Flow of Clinic & Patient Allocation.



Abbreviation: CME, Continuing Medical Education

[a]Due to sequestration of the data, neither the intervention assignment nor the number of patients is available for excluded clinics.

[b]Evaluability exclusion counts may overlap (patients can fail multiple criteria).

Figure 5:
Clinical Workflow for Blood-based Testing

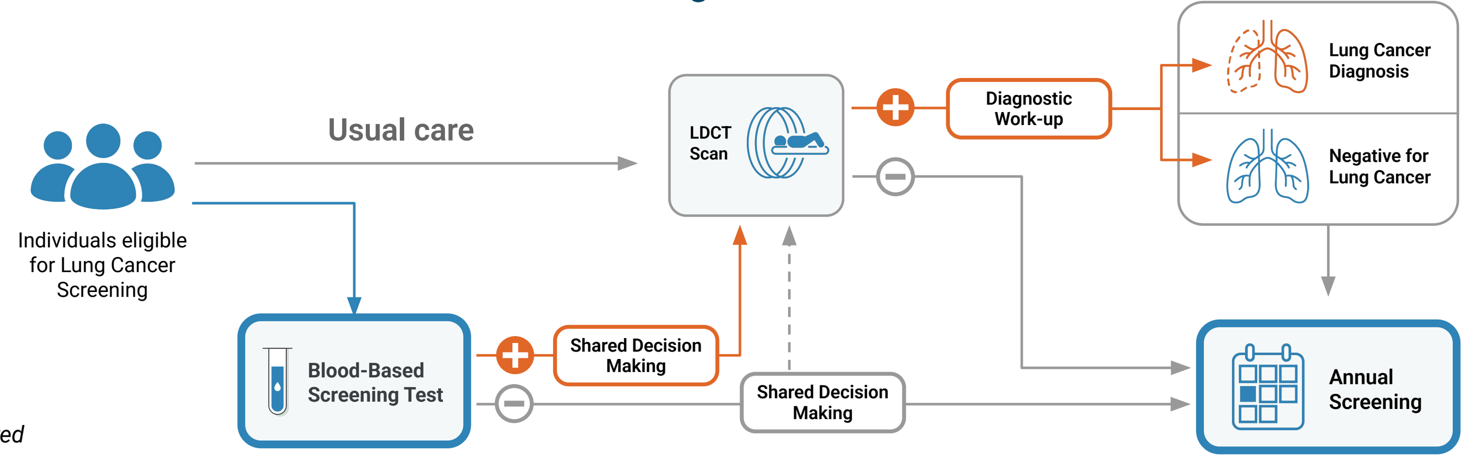


Table 1:
Clinic Characteristics Balanced Between Arms

Geographic regions are largely urban; enrollment clinics were selected for catchment areas of high socioeconomic diversity[6]

Clinic and Patient Characteristics Overall and by Analytic Allocation	N (%)	Arm Assignment	
CLINIC CHARACTERISTICS	Overall, N = 28	Usual Care (Arm A)[a], N = 15	Intervention (Arm B), N = 13
Health Network, n (%)			
Network 1	20 (71%)	10 (67%)	10 (77%)
Network 2	8 (29%)	5 (33%)	3 (23%)
Geographic Region, n (%)			
Urban	26 (93%)	13 (87%)	13 (100%)
Rural	2 (7%)	2 (13%)	0 (0%)
Patients per Clinic, Median (IQR)	85.5 (52.5 -141.8)	89.0 (64.5 -133.5)	79.0 (34.0 -139.0)
Clinicians per Clinic, Median (IQR)	8.0 (4.8 - 11.0)	7.0 (4.5 -10.5)	9.0 (6.0 - 11.0)

Table 2:
Patient Lung Cancer Screening History Overall and by Analytic Allocation: Balanced Between Arms

The Study Included Only Patients That Were Behind On Screening

Patient Characteristics Overall and by Analytic Allocation	N (%)	Arm Assignment	
EVALUABLE PATIENT CHARACTERISTICS	Overall, N = 2,953	Usual Care (Arm A)[a], N = 1,662	Intervention (Arm B), N = 1,291
LDCT Screening History			
Behind on Screening (>15 months)	222 (7.5%)	134 (8.1%)	88 (6.8%)
Never Screened	2,414 (81.7%)	1,369 (82.4%)	1,045 (80.9%)
Newly Eligible, Age criteria	59 (2.0%)	31 (1.9%)	28 (2.2%)
Unknown/Missing	258 (8.7%)	128 (7.7%)	130 (10.1%)

Table 3:
Patient Characteristics Overall and by Analytic Allocation. Enrollment of Clinical Sites achieved a diverse screening population

Patient Characteristics Balanced Between Arms

IQR = Interquartile range **SD** = Standard deviation

Patient Characteristics Overall and by Analytic Allocation	N (%)	Arm Assignment	
EVALUABLE PATIENT CHARACTERISTICS	Overall, N = 2,953	Usual Care (Arm A)[a], N = 1,662	Intervention (Arm B), N = 1,291
Age, years, Mean (SD)	64.5 (7.8)	64.6 (7.8)	64.3 (7.9)
Sex, n (%)			
Female	1,512 (51.2%)	844 (50.8%)	668 (51.7%)
Male	1,441 (48.8%)	818 (49.2%)	623 (48.3%)
Race/Ethnicity[b], n (%)		High percentage of Non-Hispanic Black across both arms	
Non-Hispanic White	2,023 (68.5%)	1,188 (71.5%)	835 (64.7%)
Non-Hispanic Black	708 (24.0%)	351 (21.1%)	357 (27.7%)
Hispanic	96 (3.3%)	62 (3.7%)	34 (2.6%)
Other	126 (4.3%)	61 (3.7%)	65 (5.0%)
Smoking Status, n (%)			
Current	1,500 (50.8%)	836 (50.3%)	664 (51.4%)
Former	1,453 (49.2%)	826 (49.7%)	627 (48.6%)
Pack-Years, Median, (IQR)	34.0 (25.0 - 45.6)	35.0 (25.0 - 46.2)	33.8 (25.0 - 45.0)
Years Since Quit (Former smokers), Mean (SD)	7.5 (4.3)	7.5 (4.3)	7.5 (4.3)
Chronic Obstructive Pulmonary Disease (COPD), n (%)	1,368 (46.3%)	770 (46.3%)	598 (46.3%)
Cardiovascular Disease, n (%)	1,361 (46.1%)	760 (45.7%)	601 (46.6%)
Asthma, n (%)	567 (19.2%)	295 (17.7%)	272 (21.1%)

Abbreviations
CI = Confidence Interval
CME = Continuing Medical Education
COPD = Chronic Obstructive Pulmonary Disease
HR = Hazard Ratio
IQR = Interquartile range
LCS = Lung Cancer Screening
LDCT = Low-dose computed tomography
NH = Non-hispanic
NPV = negative predictive value
SD = Standard deviation
USPSTF = United States Preventive Services Task Force

Figure 6:
Blood-Based Testing Resulted in Clinically Meaningful Increase in Any Lung Cancer Screening (LCS) and Screening by LDCT

Cumulative incidence of study outcomes over time; point estimate shown at 11 months.
The P values refer to the strength of the association in the pre-specified multivariable test of each hypothesis

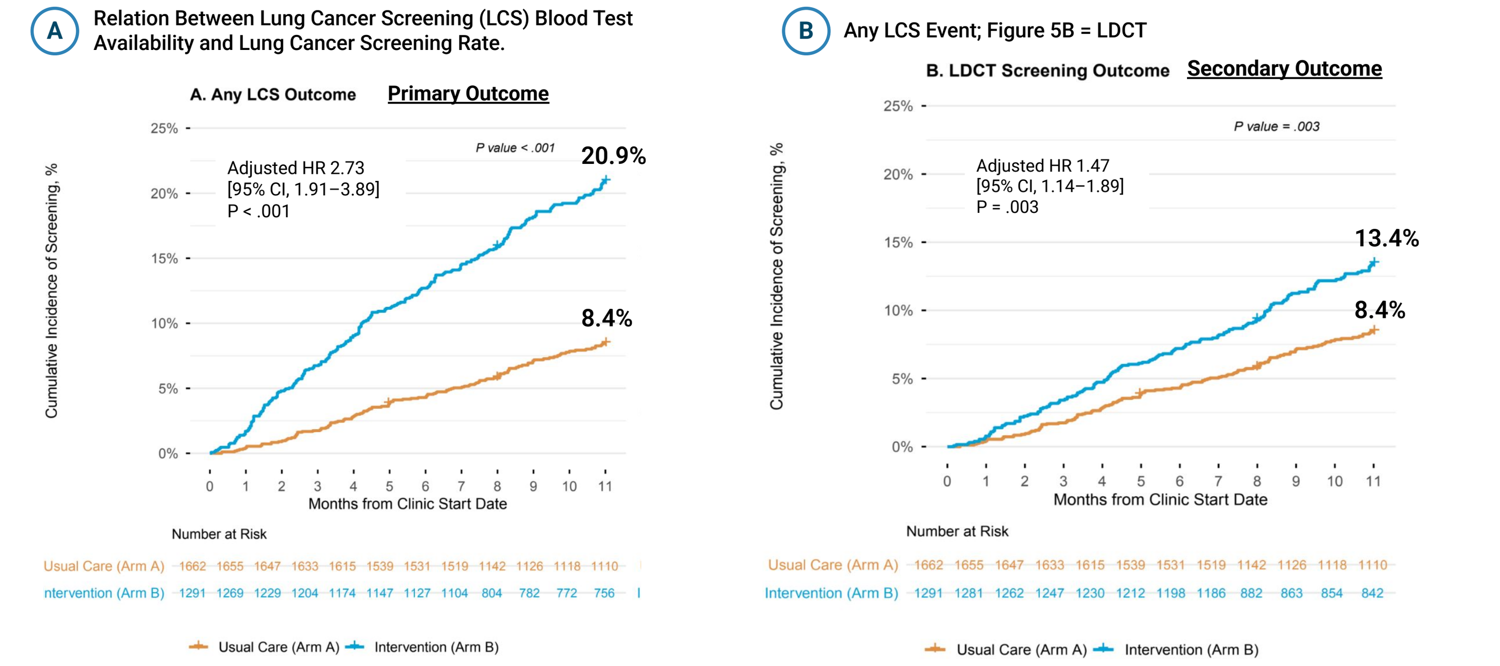
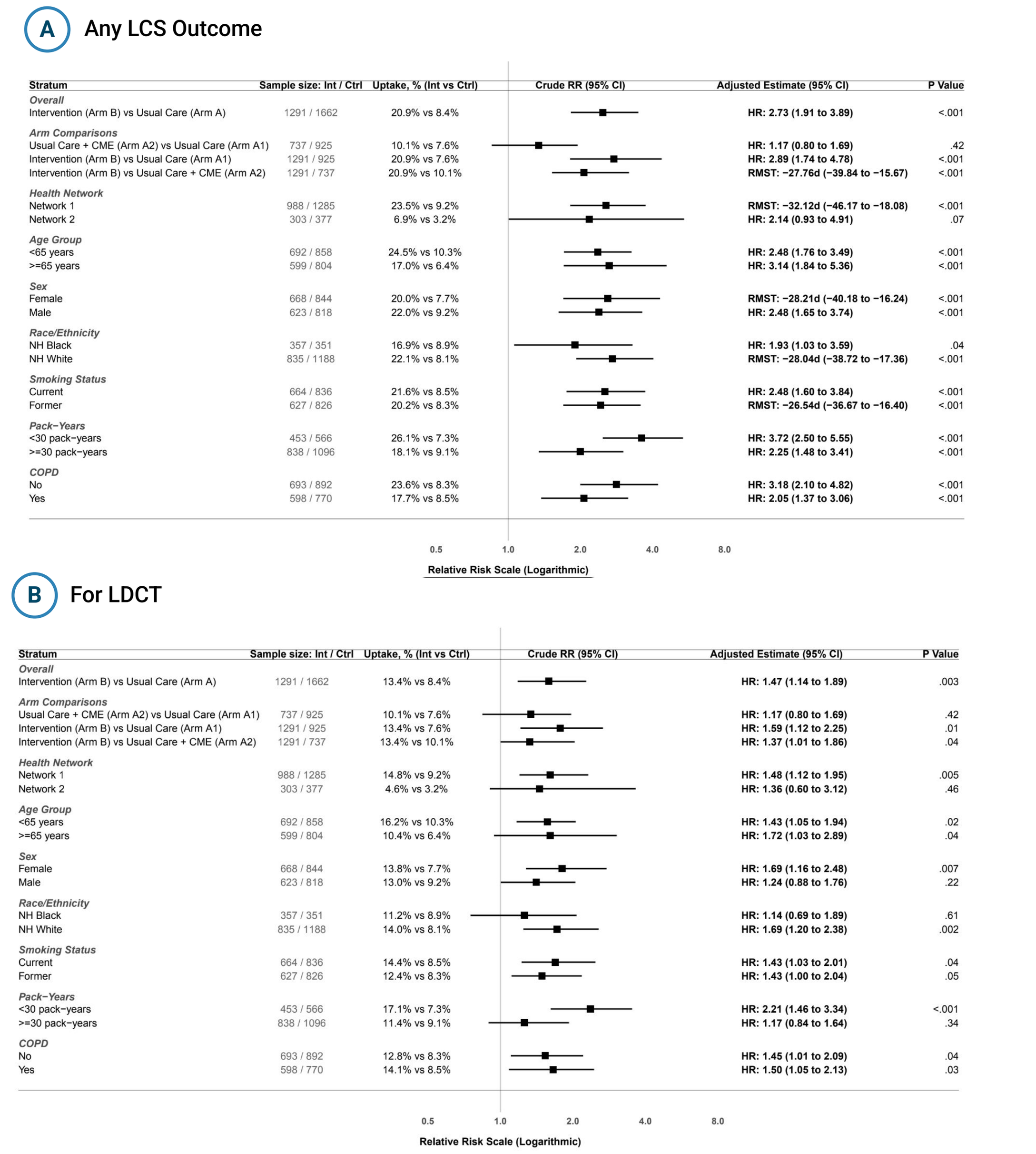


Figure 7:
Observed and Adjusted Effect Sizes Across Subgroups of Interest

Screening Uptake Benefit Is Broadly Consistent Regardless of Patient Subgroup

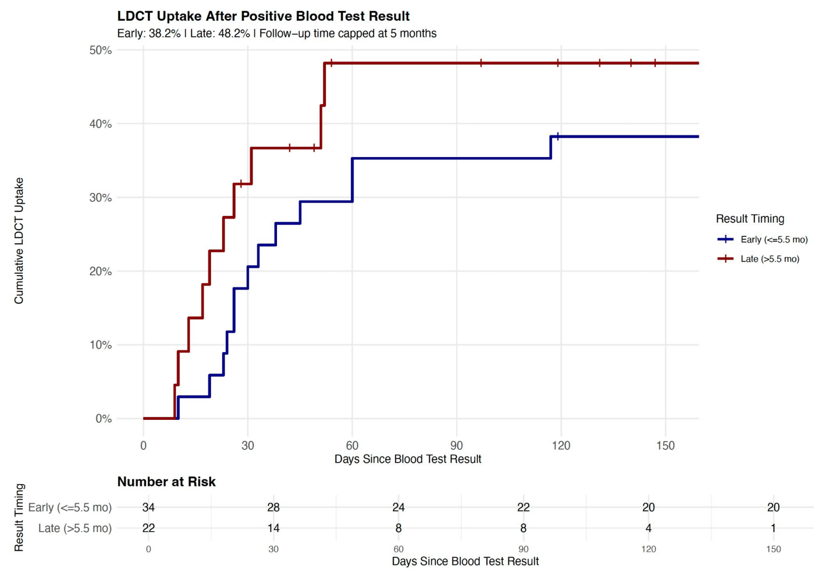
Benefits of the intervention are robust for both primary and secondary outcome across: Network, Age, Sex, Race/ethnicity, Smoking history, smoking intensity, comorbidity subgroups
The effect was not impacted by CME education in the control Arm A2.



Abbreviations: LCS, lung cancer screening; Ctrl, control arm; Int, intervention arm; RR, risk ratio; CI, confidence interval; HR, hazard ratio; CME, continuing medical education; RMST, restricted mean survival time; d, days; LDCT, low−dose CT; NH, Non−Hispanic; COPD, Chronic Obstructive Pulmonary Disease.

Figure 8:
Cumulative Incidence of LDCT Following Return of a Positive Blood-based Test Result, Stratified by Timing of Blood Test Result

Clinical Follow-up for positive blood-based testing results



Data indicates that there is a "learning curve" with higher follow through in the 2nd half of the study:

Estimated cumulative incidence: Early Adopter (blue line), 38.2% (95% CI, 19.5%–52.6%); Late Adopter (red line), 48.2% (95% CI, 20.8%–66.1%). 95% CIs derived via cluster bootstrap resampling.

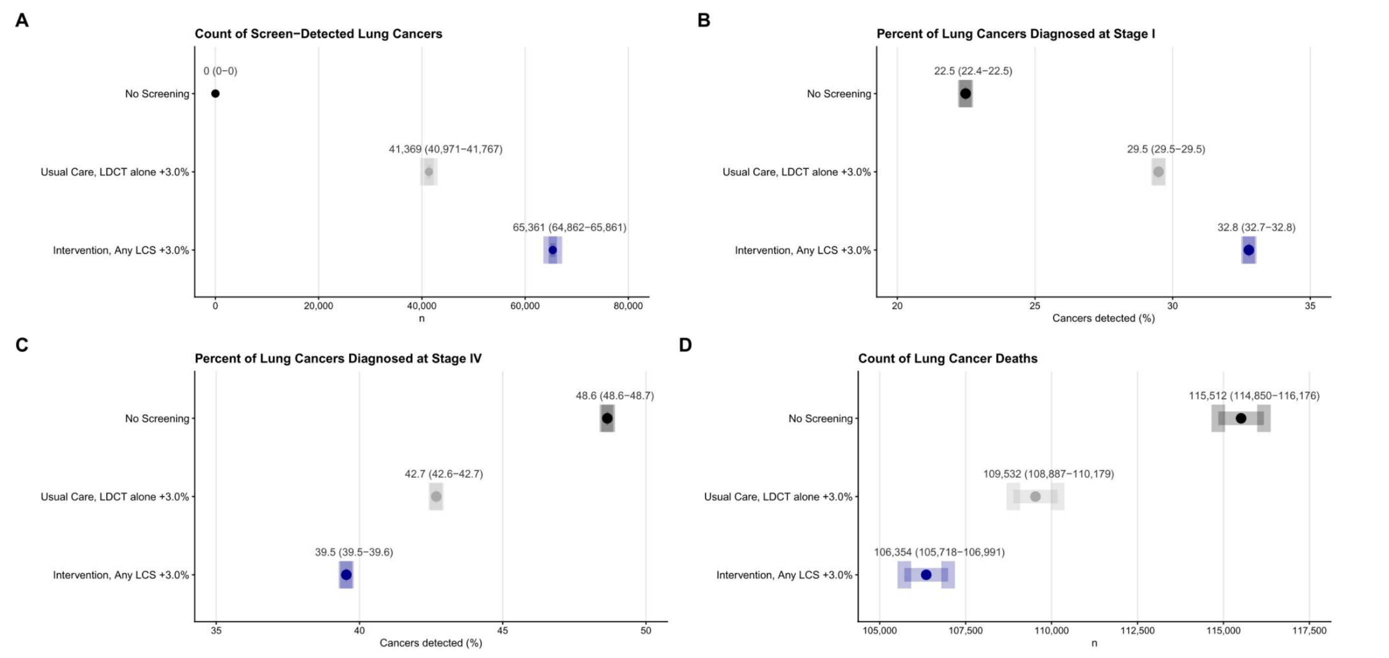
Overall cumulative incidence of LDCT following return of a positive blood-based screening test result, stratified by Result:
Negative blood test → 5.6% (95% CI, 1.5%–13.0%) go on to LDCT
Positive blood test → **42.4%** (95% CI, 31.2%–55.9%) go on to LDCT

These rates are similar to the early data on colonoscopy rates following positive stool-based testing results for colorectal cancer screening.[8]

Figure 9:
Projected 5 year Population Health Impact of LCS Blood-based Test Availability in Primary Care Clinics

Impact of blood-based screening vs LDCT only:

- Increases number of cancers detected
- Increases percent of Stage I detected cancers
- Decreases percent of stage IV lung cancers
- Averts ~3,178 additional deaths due to lung cancer



Modeled with 0.7% lung cancer prevalence, 24% LDCT false-positive rate,[7] 80% and 56% LCS blood test sensitivity and specificity.
3.0% hypothetical annual increase for both usual care and blood-based cancer screening
Method: The model is previously described in Mazzone et al[4]. Trial results were applied in Monte Carlo simulations to a base population of the 13 million currently eligible but unscreened or underscreened Americans[3]. Outcomes, including lung cancer screenings, lung cancer diagnosis by stage, and deaths due to lung cancer, were probabilistically generated. The population was cycled and aged in annual increments over 5 years.

Availability of Blood-based Screening increased Lung Cancer Screening rates with a modeled 5 year potential to avert more deaths

Primary Outcome: Any Lung Cancer Screening	Secondary Outcome: LDCT Screening	LDCT Follow-up after Blood-based Testing	Projected Population Health Impact
2.73X Screening Rate Increase	**1.47X** LDCT Rate Increase	Post-positive result LDCT follow-up **42.4%**	**~3,178** Lung Cancer Deaths Preventable
Any LCS: 20.9% (intervention) vs. 8.4% (usual care)	**LDCT:** 13.4% (intervention) vs. 8.4% (usual care)	Post-negative result LDCT follow-up **5.6%**	Projected over 5 years, among 13 million simulated individuals, with 3% annual uptake increase (1,896–4,461)
Adjusted HR 2.73; P < .001	Adjusted HR 1.47; P < .003		Potential to avert an average of ~3178 more deaths than LDCT Only*

28 clinics and 2,953 patients who were behind on lung screening recommendations
*LDCT only: averted average of 5,980 deaths compared to No Screening
Any LCS: averted average of 9,158 deaths compared to No Screening

CONCLUSIONS

In this Cluster randomized trial of 28 clinics and 2,953 patients who were behind on lung screening recommendations, blood-based screening meaningfully increased Lung Cancer Screening rates. A 5 year modeled outcomes analysis reveals potential to avert ~3178 more deaths than by LDCT only.

1. The availability of a blood-based test significantly increased overall screening rates (20.9%) and low-dose CT rates (13.4%) compared with usual care (8.4%).
2. The effect is consistent across subgroup stratifications.
3. Post-positive clinical follow-up of 42.4% without dedicated navigation programs, sustained education or a focus on program efficiencies.
   - Similar to rates of follow-up during early implementation of stool-based testing for Colorectal Cancer screening.[8]
4. Conservative 5 year outcomes modeling suggests that an average of 3,178 (1,896 – 4,461) more deaths due to lung cancer can be averted with access to this blood-based testing approach compared to LDCT only, assuming stable or modestly increasing screening uptake, respectively.

Given the low rates of lung cancer screening via LDCT, access to a lung cancer screening blood test, such as the pWGFrag-Lung test, could substantially increase LCS rates and reduce lung cancer mortality.