CASCADE-LUNG: Validation of a blood-based assay that evaluates cell-free DNA fragmentation patterns to detect lung cancer

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BACKGROUND Despite longstanding national recommendations for lung cancer screening by low-dose computed tomography (LDCT), annual participation rates are below 15%.[1-3] Cost, access, and uncertainty over individual-level benefits and harms of screening preclude greater uptake.[4,5] The development of a low-cost initial blood test that detects lung cancer with high sensitivity could boost LDCT screening rates and improve screening efficiency, by identifying within the screening-eligible population those at relatively higher risk of lung cancer. DELFI (DNA evaluation of fragments for early interception) is a technology that uses low-coverage, whole-genome sequencing and machine learning to detect cancer signals in the blood. In an early study, DELFI demonstrated high sensitivity to detect stage I/II lung cancers.[6] CASCADE-LUNG (NCT05306288) is an ongoing study to clinically validate a DELFI-based test to detect lung cancers that would be found by chest LDCT.

1. USPSTF, et al. *JAMA*. 2021;325(10):962-70. 2. Pham D, et al. *Clin Lung Cancer*. 2020;21(3):e206-11. 3. American Lung Association. State of Lung Cancer 2022 Report. 4. Wang GX, et al. *Radiology*. 2019;290(2):278-87. 5. Jonas DE, et al. *JAMA*. 2021;325(10):971-87. 6. Mathios D, et al. *Nat Commun*. 2021;12(1):5060.

CASCADE-LUNG (NCT05306288): Cancer Screening Assay Using DELFI: A Clinical Validation Study in Lung

ELIGIBILITY CRITERIA

Inclusion criteria:

- Age ≥50 years
- Current or previous smoking history of ≥20 pack-years
- Initial or annual follow-up lung cancer screening chest CT planned/scheduled within 30 days after enrollment

Exclusion criteria:

- Evidence of any diagnosed cancer (including lung cancer) other than nonmelanoma skin cancer or carcinoma in situ within 2 years prior to enrollment
- Prior systemic therapy, definitive therapy, radiation, or surgical resection for any cancer diagnosis within 2 years prior to enrollment (except surgery for nonmelanoma skin cancer and biopsies)
- Any history of hematologic malignancies or myelodysplasia within 2 years prior to
- Blood product transfusion within 120 days prior to enrollment

OBJECTIVES AND ENDPOINTS

Objectives:

- To evaluate the sensitivity and specificity of the DELFI lung cancer screening test for detection of lung cancer, using the reference method of chest CT at enrollment with pathological diagnosis in the overall study population (primary) and in clinically relevant subgroups of interest (secondary)

Endpoint:

- Presence or absence of pathologically confirmed lung cancer as determined by diagnostic resolution achieved from the time of the enrollment chest CT scan through follow-up

ANALYSIS PLAN

Primary analysis:

- The sensitivity and specificity of the DELFI lung cancer screening test will be estimated.
- Additional predictive performance metrics will be calculated: positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio.
- Two-sided 95% confidence intervals will be constructed for these metrics.

Subgroup analyses:

- Performance of the DELFI lung cancer screening test in clinical subgroups of interest will be evaluated, including, but are not limited to, the following: cancer stage; cancer histology (NSCLC *vs* SCLC; NSCLC histological subtypes); previous cancer history; family history of lung cancer; USPSTF lung cancer screening criteria (2013 *vs* 2021; eligible vs ineligible); smoking status; COPD status; age; sex; race and/or ethnicity; initial screen *vs* annual screen.

≥50 years of age
Current or previous smoking history of ≥20 pack-years
Planned CT scan for lung cancer screening

↓

Blood sample collection[a]

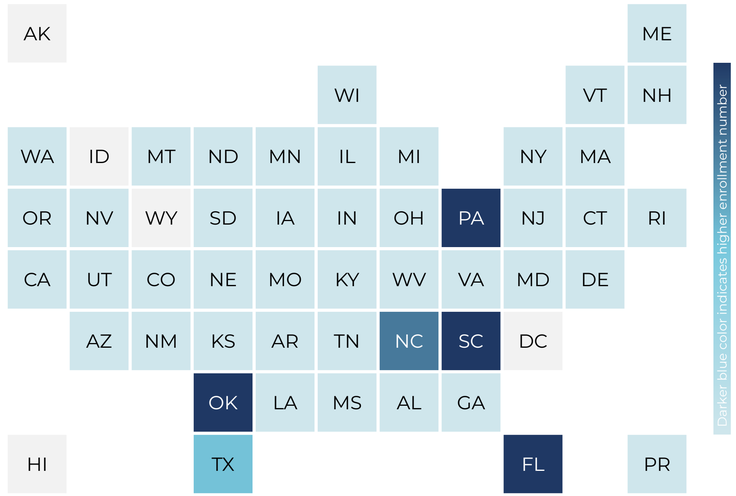
↓

CT scan within 30 days after enrollment

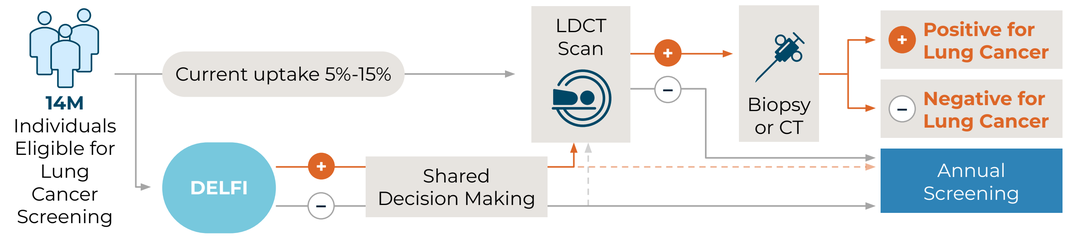
- Suspicious nodules[b] → **Medical record review at 4 months after enrollment** → **Medical record review at 12 months after enrollment**
- No suspicious nodules[b]

[a]N≈15000; Enrollment until 70 patients with pathologically confirmed lung cancer and blood sample acceptable for DELFI analysis, based on 0.6% estimated rate of lung cancer diagnosis
[b]Suspicious nodules defined as: LungRADS category of 4A or higher reported on enrollment chest CT scan; follow-up recommended within 3 months of the enrollment chest CT scan; LungRADS category not reported and ≥6 mm lung nodule(s) identified on the enrollment chest CT scan

CURRENTLY ENROLLING IN ACADEMIC AND COMMUNITY SITES ACROSS THE US



Development and validation of a noninvasive, accurate, low-cost DELFI test has the potential to improve lung cancer screening among high-risk individuals, by identifying those more likely to benefit from screening, thereby reducing harms and boosting uptake of lung cancer screening.



The DELFI test has the potential to—

- Stratify a heterogeneous screening-eligible population into groups with relatively higher and lower risk
- Provide genomic data to inform shared decision making
- Promote more judicious use of LDCT in healthcare resource-constrained settings

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DELFI