

# Early-stage Lung Cancer Liquid Biopsy based on Automated EV-SERS-AI System

: A Retrospective and Prospective Multi-ethnic Clinical Trial

Partnering with



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## Abstract

Lung cancer, a leading cause of cancer-related death, is often underdiagnosed by current liquid biopsy methods due to biomarker variability and tumor heterogeneity. This study reports clinical trial results of a liquid biopsy platform that combines extracellular vesicle analysis with SERS and AI, enabling accurate, non-invasive detection of early-stage lung cancer in cohorts from Korea and the U.S.

## Introduction

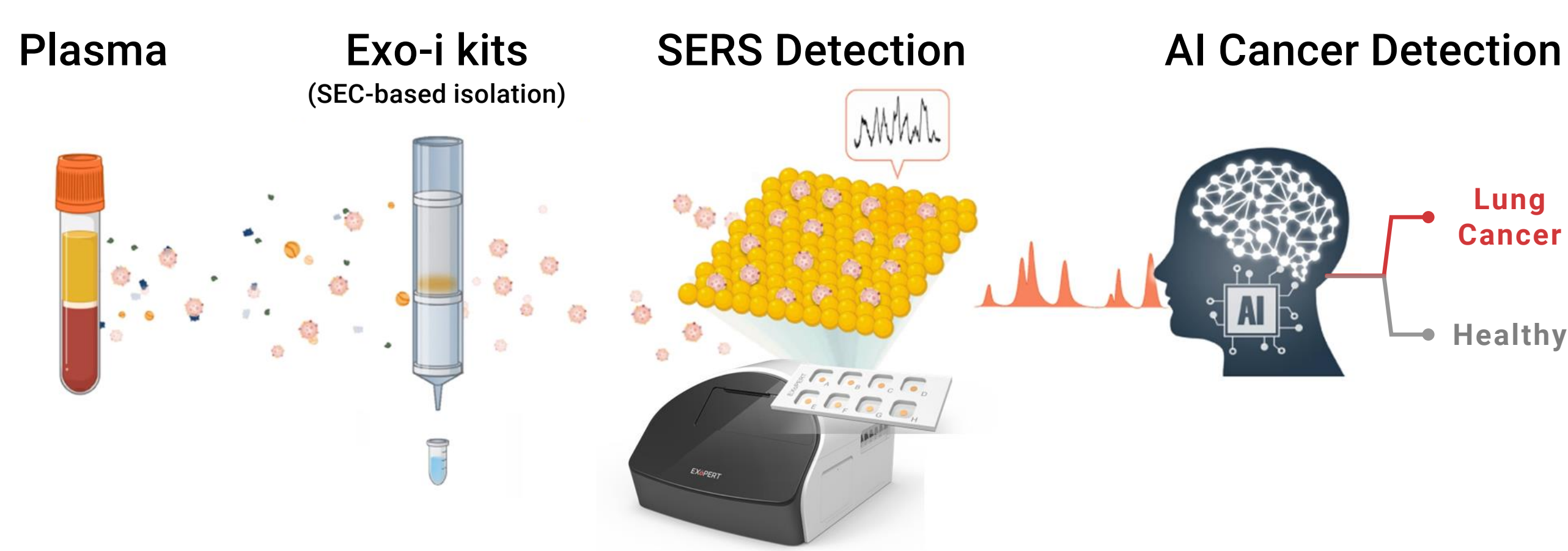


Figure 1. Schematic image of EV-SERS-AI diagnostic system.

- Surface-enhanced Raman spectroscopy(SERS) amplifies potential cancer-related molecules present on the surface of EVs
- Although EV spectrums are complex and heterogeneous, deep learning algorithms can be trained to extract cancer-specific features.
- To evaluate the performance of our system, two clinical studies were conducted—one in South Korea and one in the United States.
- The South Korean study was a retrospective analysis involving approximately **1,800 subjects from 11 hospitals**, including patients with non-lung cancers and non-malignant pulmonary diseases (e.g., pneumonia, lung nodules, and other interstitial lung diseases with fibrosis), to assess cross-reactivity.
- The international study was conducted across **5 institutions in the U.S.**, with retrospective data collected from 2 sites and **prospective data from 4 sites.**

### Study Demography

	Trial in South Korea	Trial in the U.S
Healthy control	466	105
Lung Cancer	587	42
Breast Cancer	168	Liver Cancer 25
Colon Cancer	171	Prostate Cancer 45
Eso-Gastric Cancer	155	Ovarian Cancer 27
Liver Cancer	60	Excluded 5
Pancreas Cancer	60	Sum 244 / 249
Prostate Cancer	4	
Lung Other Disease	91	
Excluded	124	
Sum	1762 / 1886	

### Inclusion criteria

- Individuals age over 50 with average risk of lung cancer who have no history of cancer.
- Subjects who are willing and able to provide written informed consent.
- Subjects who are willing and able to comply with the study requirements.
- (Intended use) Subjects aged 50 years or older with a confirmed diagnosis of lung, liver, prostate or ovarian cancer through medically established conventional diagnostic procedures.
- (Intended use) Subjects who have not received any chemical and radiological treatment for cancer.

### Exclusion criteria

- Subjects who have been previously diagnosed with another form of cancer other than trial's designated targets.
- Subjects who have not received any chemical and radiological treatment or surgery for cancer.
- Subjects with severe co-morbidities/uncontrolled disease.
- Subjects who have received a solid organ transplant.
- Subjects who have been diagnosed with dementia or neurological disease.
- Subjects who have been diagnosed with or have a known history of drug abuse
- Subjects who are pregnant or breastfeeding.
- Subjects who have consented and have undergone treatment in any other clinical trial within the past 6 months.
- Subjects who have received treatment related to pulmonary nodules, such as antibiotics or hormones prior to entering the study.

### Collection sites

(KR) Gangnam Severance Hospital, Korea Univ. Guro Hospital, Seoul National Univ. Bundang Hospital, Samsung Medical Center, Asan Medical Center, Ajou Univ. Hospital, Korea Cancer Centre Hospital, Chungbuk National Univ. Hospital, Inje Univ. Paik Hospital, Kyungpook National Univ. Hospital, Soonchunhyang Univ.Hospital

(US) ResearchTrialGroup, Univ of Louisville Hospital, City of Hope Hospital, INOVA, MT Group

Table 1. Demography, Inclusion and exclusion criteria, and collections sites.

## Method

### EV isolation

- EVs were isolated from plasma using **Exo-i**; dual-size exclusion chromatography (SEC) kit with automated EV collector, **Excelerator™** device.

### Signal Detection

- SERS signal detection was performed using **ARM™Dx**. To reflect EV heterogeneity, signals were collected from 100 spots per sample.

### AI Analysis

- Our CNN-based algorithm includes **EV signal filtering, cancer classification, and score refinement.**
- The final score is based on 100 signals. Of 2,006 samples, 1,391 were used for training, and in the U.S. study, 109 of 244 samples for fine-tuning. A sample-wise data split ensured reliability.

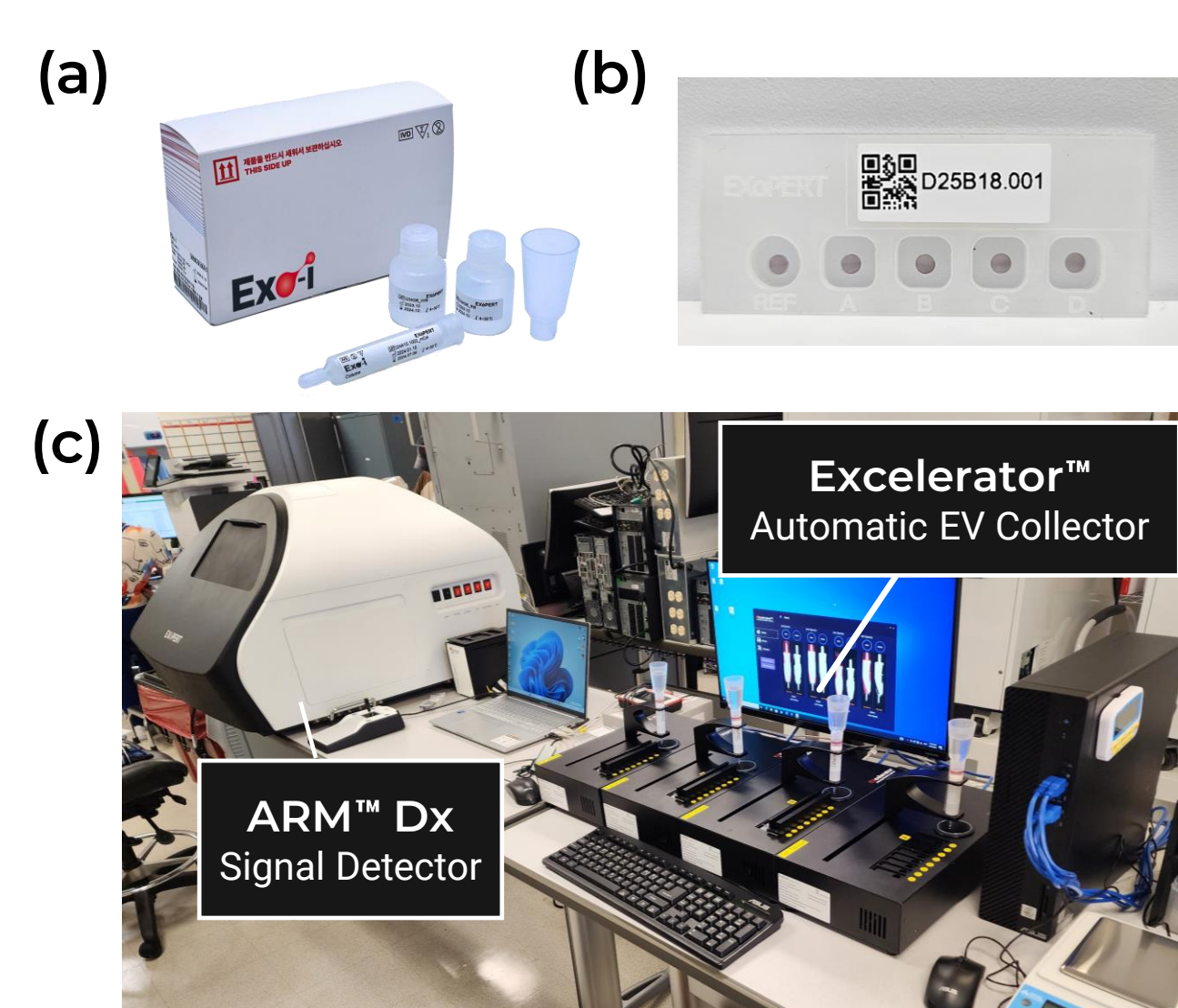


Figure 2. (a) Exo-i kit (b) SERS detection chip (c) clinical trial setups at external lab

## Result

### Non-EV signal filtering

- Non-EV signals (e.g., blank, diluted, low-EV samples, PBS) were used to develop filtering system.
- The EV-filtering model was validated in a blind test with 96% accuracy .
- Samples with over 50 of 100 signals identified as EV were considered EV-positive.

Sample Type	EV counts /100 signal	Accuracy
Human Plasma derived EV	78.6	7/8
Pooled Plasma derived EV	70	4/4
Raw Pooled Plasma	4.1	4/4
Pooled Plasma EV diluted x100	4.3	4/4
PBS	1.9	8/8
Blank	3.3	4/4
Sum	31/32	

Table 2. Non-EV signal filtering model performance

### Cancer Signal Detection

- The clinical results are from a validation cohort of 135 U.S. subjects, including healthy controls (n = 56), lung cancer patients (n = 24; *early stage I-II, n = 13; advanced stage III-IV, n = 11*), and patients with other cancers (n = 55; *prostate, n = 22; ovarian, n = 16; liver, n = 17*). See clinical specificity below.

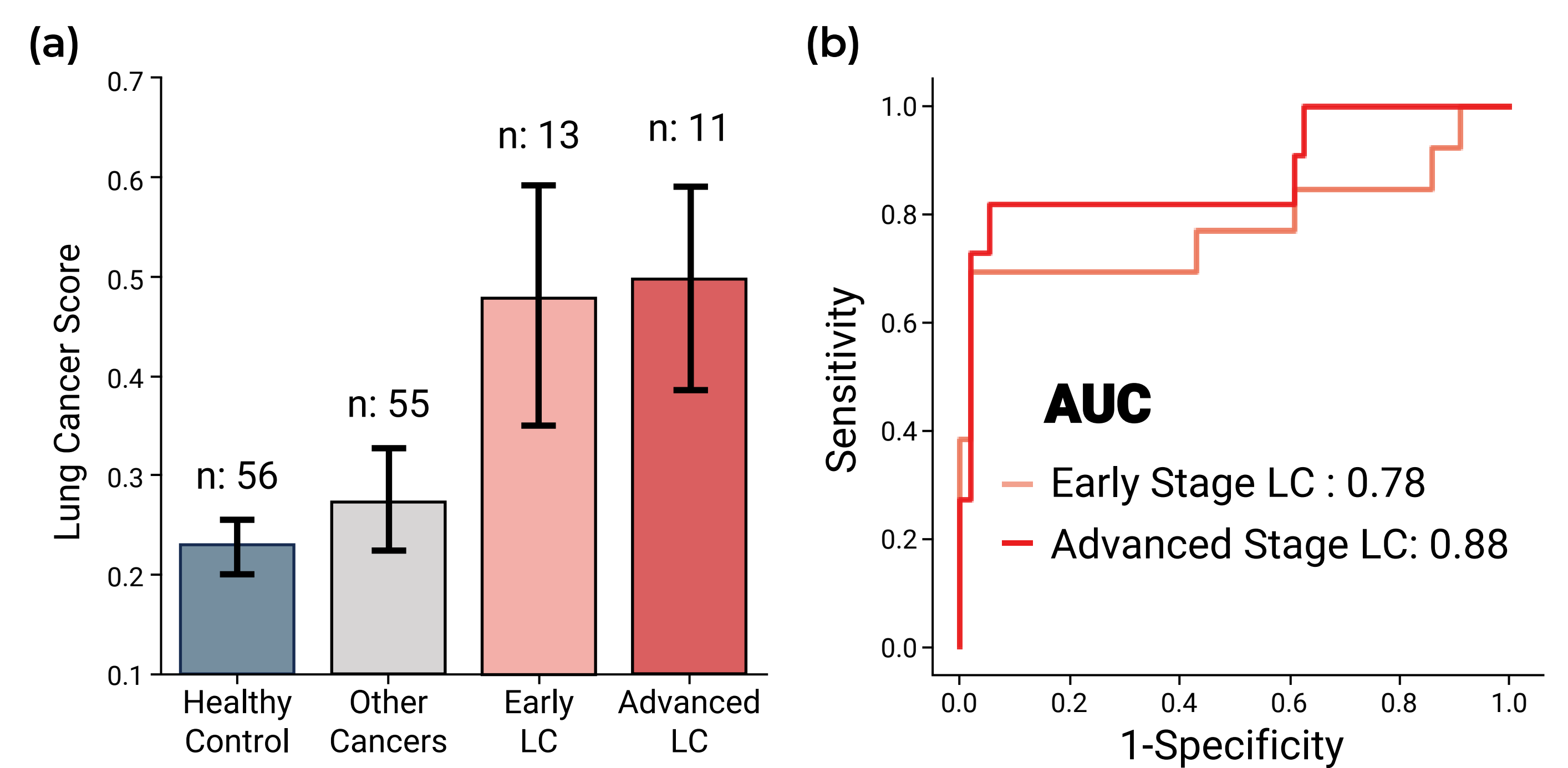


Figure 3. (a) Final scores from the diagnostic model. (b) ROC curves comparing healthy controls with early- and advanced-stage lung cancer. (LC) patients.

	Lung Cancer	Healthy Control
Total N	24	56
Mean	0.49	0.23
Std	0.21	0.11
% Called Pos/Neg	75.0 / 25.0	5.36 / 94.9

Sensitivity	0.750 (0.533 - 0.902)
Specificity	0.946 (0.851 - 0.989)

(95% CI ; based on Clopper-Pearson method)

Table 3. The U.S. trial study result summary.

- The algorithm's prediction on our 135 hold-out test set achieved a sensitivity of 75% and specificity of 95%. **Sensitivity by cancer stage was 69% for early-stage and 82% for advanced stage.**
- The average false positive rate across 73 subjects with **non-lung cancers** (breast, prostate, ovarian, liver, and stomach) was 30%, ranging from 0% to 50% by cancer type.
- The false positive rate for individuals with **lung diseases other than lung cancer** (lung nodules and interstitial pulmonary diseases with fibrosis) was 17% among 42 subjects, primarily driven by the presence of lung nodules.

	Breast Cancer	Prostate Cancer	Ovarian Cancer	Liver Cancer	Stomach Cancer	Lung Nodule	Other*
Called Negative	4	21	8	17	6	20	15
Called Positive	0	5	8	0	4	6	1
FPR	0.00	0.19	0.5	0.0	0.40	0.23	0.06

\* Other interstitial pulmonary diseases w/ fibrosis

Table 4. Cross-reactivity in cancers other than lung cancer and non-cancerous lung diseases, based on results from the U.S. and South Korea trials.

## Conclusion

We implemented and validated a novel liquid biopsy system for lung cancer, from EV isolation to signal detection. We evaluated clinical performance on multi-ethnic samples, demonstrating high predictive accuracy for early lung cancer detection. These results highlight the system's potential as a new screening approach.

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