Assessing the Cancer Risk of Lung Nodules by Proteomic or Gene Expression Panels

Matthew Smeltzer, PhD

Associate Professor of Epidemiology

University of Memphis

Outline

1. The problem
2. Potential Solutions
3. The Promise of Proteomics and Gene Expression
4. Deep learning?
5. How do we achieve broad implementation?

1. The Problem

- The mortality burden of lung cancer is high
- Early detection of cancerous lung nodules can save lives.
- However, most lung nodules are not cancer.

We need better tools to:

- Improve the selection of individuals undergoing screening

- Assess the cancer risk of undetermined nodules that have been identified

2. Potential Solutions

What options do we have to assess the cancer risk of nodules that have been identified?

- Clinician Determination
- Clinical Models
- Proteomics or Genomics
- AI or deep learning

3. Proteomics and Gene Expression

- PANOPTIC Trial (Pulmonary Nodule Plasma Proteomic Classifier) - A prospective, multicenter trial (N= 685) with 8- to 30-mm lung nodules
- LG3BP + C163A
- Evaluated the accuracy of an integrated proteomic classifier in identifying benign nodules in patients with a pretest probability of cancer <= 50%.
- Results were integrated with a clinical risk prediction model to identify likely benign nodules.

Silvestri GA, Tanner NT, Kearney P, Vachani A, Massion PP, Porter A, Springmeyer SC, Fang KC, Midthun D, Mazzone PJ; PANOPTIC Trial Team. Assessment of Plasma Proteomics Biomarker's Ability to Distinguish Benign From Malignant Lung Nodules: Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial. Chest. 2018 Sep;154(3):491-500.

PANOPTIC: LG3BP + C163A

Two-protein biomarker ratio combined with a lung nodule clinical risk predictor had:

97% Sensitivity
44% Specificity

40% relative reduction in invasive testing for patients with benign nodules

While potentially delaying the management of 3% of malignant nodules.

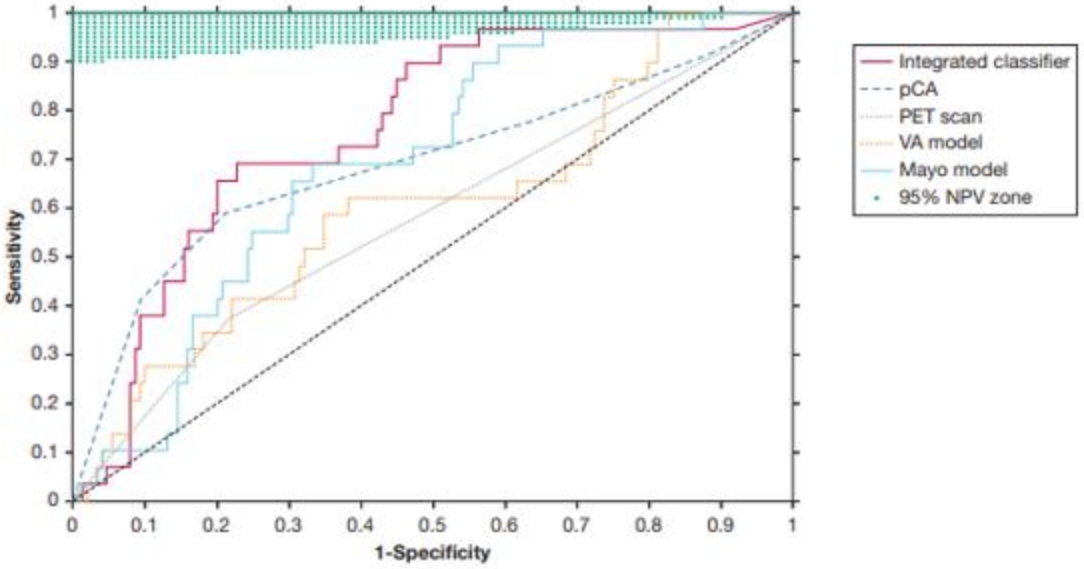


Figure 3 – *Comparison of the area under the receiver-operating characteristic curves of lung nodule malignancy risk assessment tools relative to the 95% NPV zone. Shown are the receiver-operating characteristic curves for subjects with lung nodules assigned a pCA ≤ 50% (n = 178) comparing the integrated classifier vs the physician-assigned pCA, PET, and the VA and Mayo cancer risk models. The shaded area indicates the ≥ 95% NPV diagnostic performance zone, which corresponds to the 5% cancer risk threshold specified in the CHEST guidelines for lung management. NPV = negative predictive value; VA = Veterans Affairs. See Figure 2 legend for expansion of other abbreviation.*

Approved for clinical use.

7 autoantibody Test (Murray 2010)

› Ann Oncol. 2010 Aug;21(8):1687-1693. doi: 10.1093/annonc/mdp606.

Technical validation of an autoantibod cancer

A Murray [1], C J Chapman [2], G Healey [1], L J Peek [3], G Parsons [4], D Baldw
H F Sewell [6], H A Fritsche [7], J F R Robertson [8]

Affiliations + expand

PMID: 20124350 PMCID: PMC2911202 DOI: 10.1093/annonc/mdp606

Research Article

Cancer Prevention Research

*Early*CDT-Lung: An Immunobiomarker Test as an Aid to Early Detection of Lung Cancer

Stephen Lam[1], Peter Boyle[2], Graham F. Healey[3], Paul Maddison[4], Laura Peek[7], Andrea Murray[3], Caroline J. Chapman[5], Jared Allen[3], William C. Wood[8], Herb F. Sewell[6], and John F.R. Robertson[5]

Abstract

Recent publications have reported the technical and clinical validation of *Early*CDT-Lung, an autoantibody test which detected elevated autoantibodies in 40% of lung cancers at diagnosis. This manuscript reports the results of *Early*CDT-Lung run on four new (postvalidation) data sets. The following four cohorts of patients ($n = 574$) with newly diagnosed lung cancer were identified: group 1 ($n = 122$), 100% small cell lung cancer (SCLC); group 2 ($n = 249$), 97% non-small cell lung cancer (NSCLC); group 3 ($n = 122$), 100% NSCLC; group 4 ($n = 81$), 62% NSCLC. Serum samples

‣ Tumour Biol. 2012 Apr 11;33(5):1319–1326. doi: 10.1007/s13277-012-0379-2

*Early*CDT®-Lung test: improved clinical utility through additional autoantibody assays

Caroline J Chapman [1,✉], Graham F Healey [2], Andrea Murray [2], Peter Boyle [3], Chris Robertson [4], Laura J Peek [5], Jared Allen [1,2], Alison J Thorpe [1], Geoffrey Hamilton-Fairley [2], Celine B Parsy-Kowalska [2], Isabel K MacDonald [2], William Jewell [5], Paul Maddison [6], John F R Robertson [1,2]

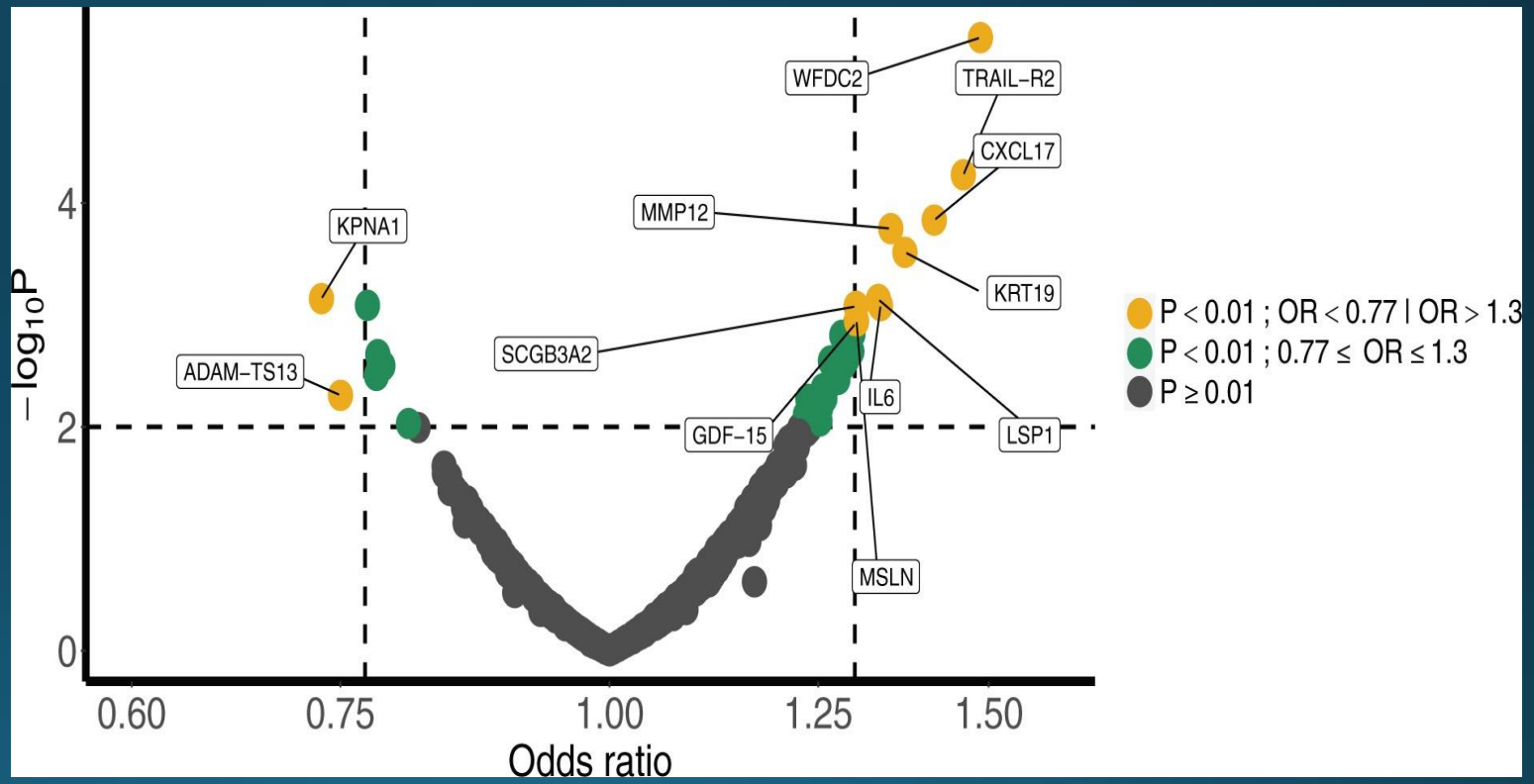
‣ Author information ‣ Article notes ‣ Copyright and License information

PMCID: PMC3460172 PMID: 22492236

Moez et al. JNCI 2023

- 4 international LDCT screening studies
- Assayed 1078 protein markers using prediagnostic blood samples from 1253 participants based on a nested case-control design.
- 36 potentially informative circulating protein markers differentiating malignant from benign nodules

Single-marker analyses of nodule malignancy.



Khodayari Moez E, Warkentin MT, Brhane Y, Lam S, Field JK, Liu G, Zulueta JJ, Valencia K, Mesa-Guzman M, Nialet AP, Atkar-Khattra S, Davies MPA, Grant B, Murison K, Montuenga LM, Amos CI, Robbins HA, Johansson M, Hung RJ. Circulating proteome for pulmonary nodule malignancy. J Natl Cancer Inst. 2023 Sep 7;115(9):1060-1070.

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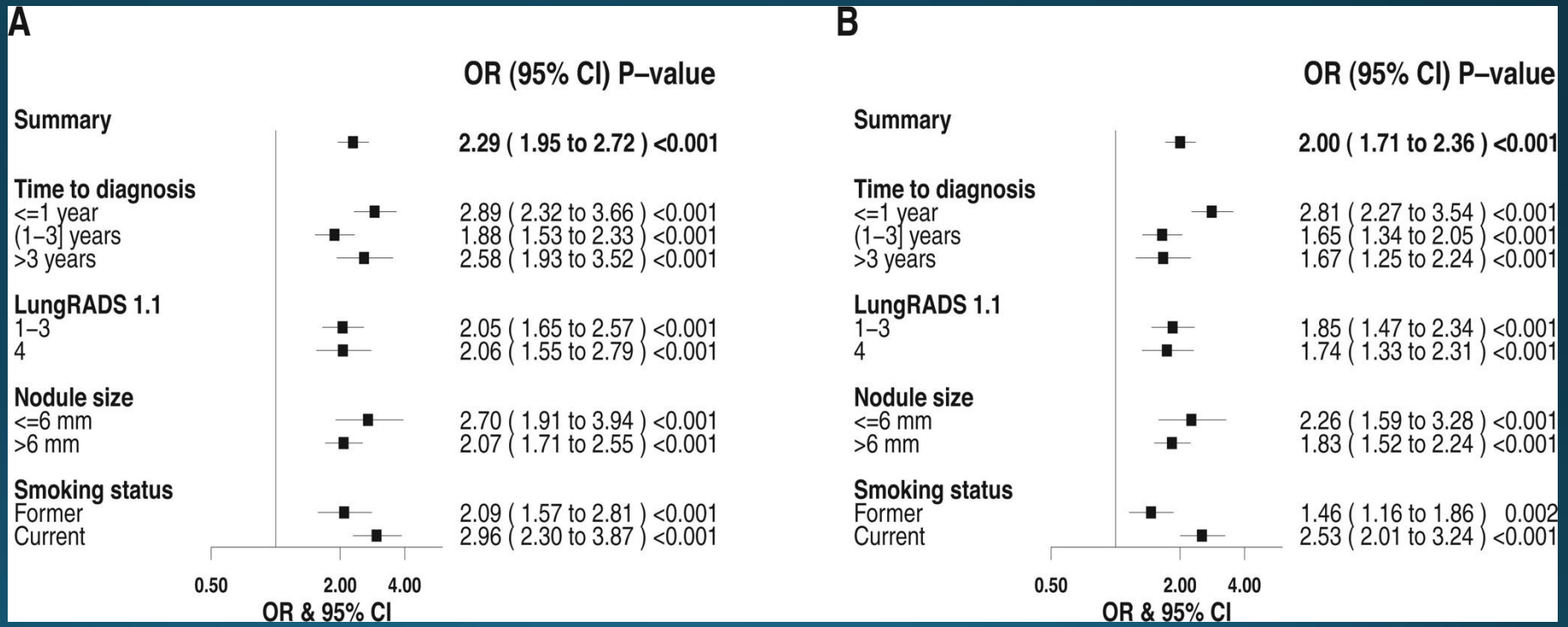
- Tightly connected biological network.
- Ten markers particularly relevant for imminent lung cancer diagnoses within 1 year

Protein burden scores illustrating the association with nodule malignancy.



Khodayari Moez E, Warkentin MT, Brhane Y, Lam S, Field JK, Liu G, Zulueta JJ, Valencia K, Mesa-Guzman M, Nialet AP, Atkar-Khattra S, Davies MPA, Grant B, Murison K, Montuenga LM, Amos CI, Robbins HA, Johansson M, Hung RJ. Circulating proteome for pulmonary nodule malignancy. J Natl Cancer Inst. 2023 Sep 7;115(9):1060-1070.

Gene Expression Panels

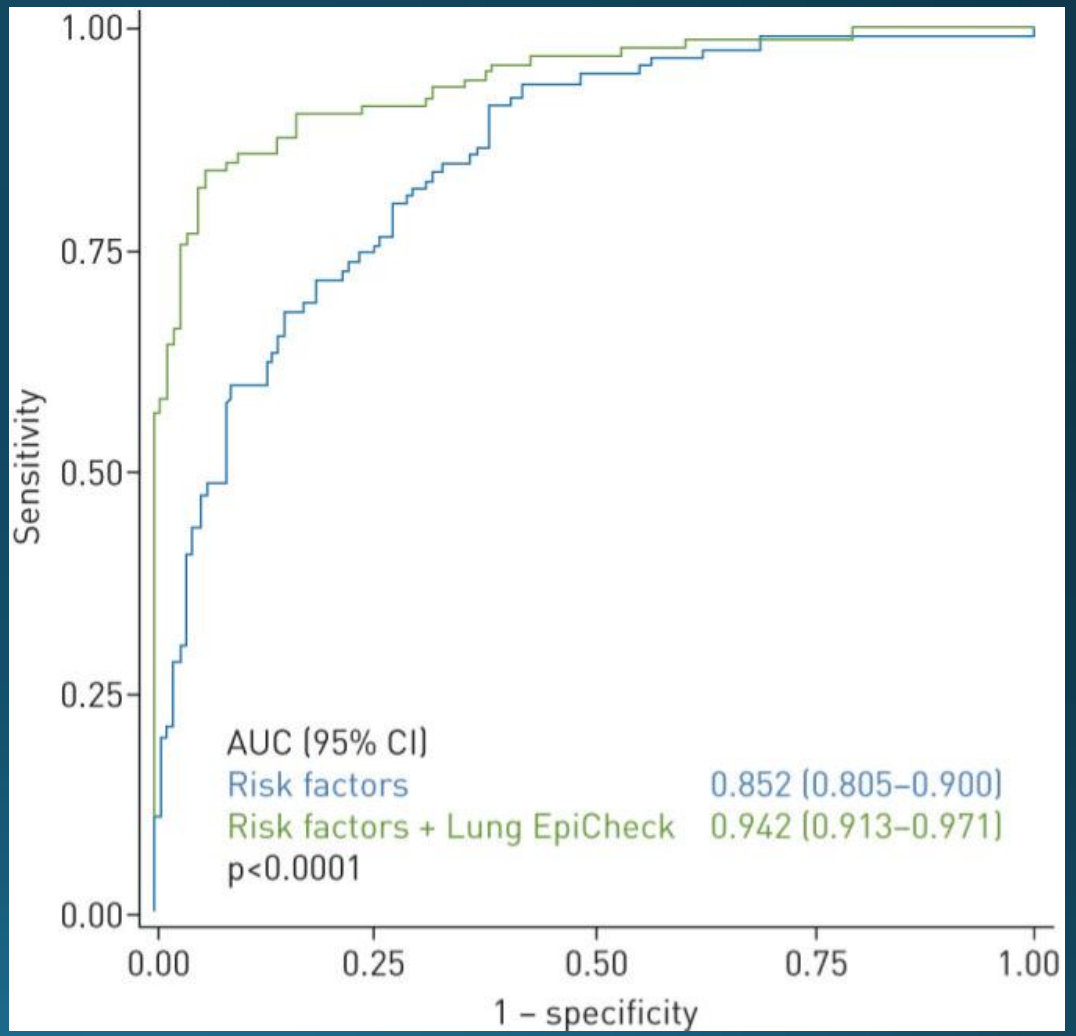
Eur Respir J. 2021 Jan 14;57(1):2002682. doi: 10.1183/13993003.02682-2020. Print 2021 Jan.

Validation of Lung EpiCheck, a novel methylation-based blood assay, for the detection of lung cancer in European and Chinese high-risk individuals

Mina Gaga [1], Joanna Chorostowska-Wynimko [2], Ildikó Horváth [3], Martin C Tammemagi [4], David Shitrit [5], Vered H Eisenberg [6], Hao Liang [7], David Stav [8], Dan Levy Faber [9] [10], Maarten Jansen [11], Yael Raviv [12], Vasileios Panagoulias [13], Piotr Rudzinski [2], Gabriel Izbicki [14], Ohad Ronen [15], Adiv Goldhaber [16], Rawia Moalem [17], Nadir Arber [18], Ilana Haas [19], Qinghua Zhou [7]

The risk factors of age, gender, smoking status, quit years, pack-years, and COPD together yielded an AUC of 0.852.

Adding six methylation biomarkers significantly increased the AUC to 0.942.



This Technology is currently under clinical investigation.

Gaga, M., Chorostowska-Wynimko, J., Horvath, I., Tammemagi, M.C., Shitrit, D., Eisenberg, V.H., Liang, H., Stav, D., Levy Faber, D., Jansen, M., et al. (2021). Validation of Lung EpiCheck, a novelmethylation-based blood assay, for the detection of lung cancer in European and Chinesehigh-risk individuals. Eur. Respir. J. 57, 2002682.

Gene Expression Panels

Cell Reports Medicine

CellPress
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Article

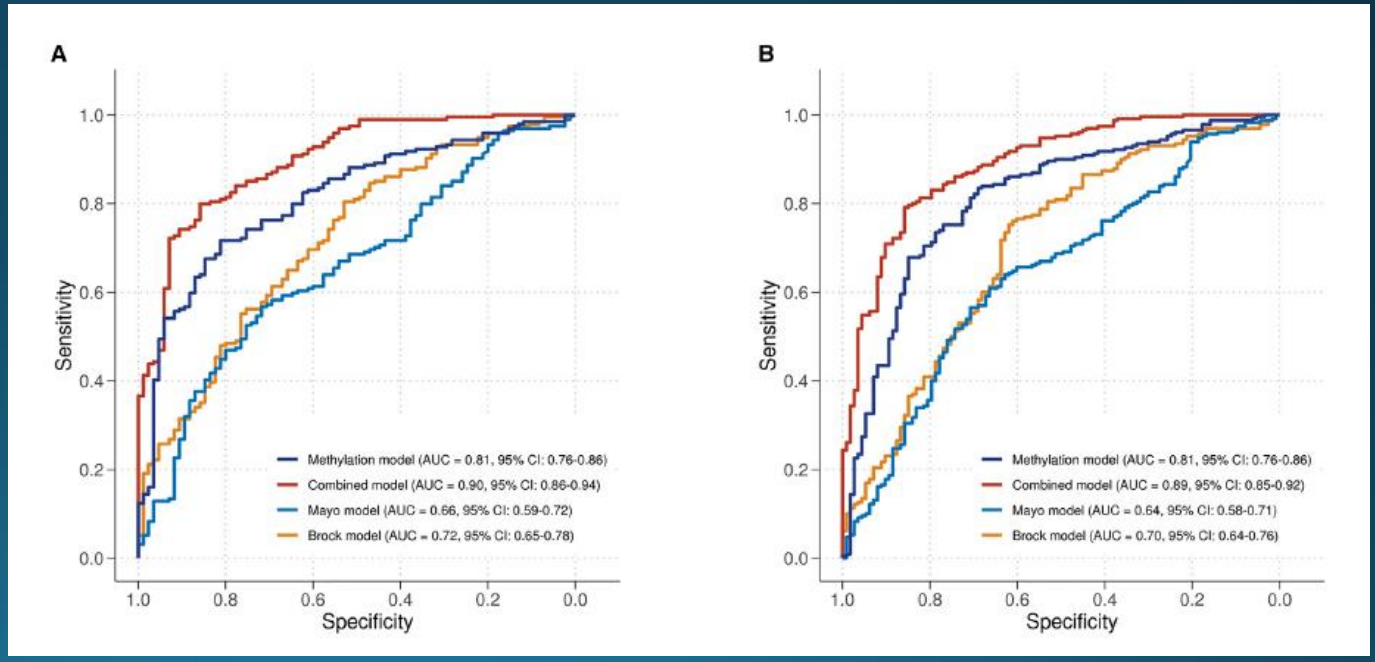
A clinically effective model based on cell-free DNA methylation and low-dose CT for risk stratification of pulmonary nodules

Wenhua Liang,[1,12,*] Jinsheng Tao,[2,12] Chao Cheng,[3,12] Haitao Sun,[4,12] Zhujia Ye,[2,12] Shuangxiu Wu,[2] Yubiao Guo,[5] Jiaqing Zhang,[6] Qunqing Chen,[6] Dan Liu,[7] Lunxu Liu,[8] Hui Tian,[9] Lin Teng,[2] Nanshan Zhong,[10] Jian-Bing Fan,[2,11,*] and Jianxing He[1,13,*]

An Oct 2024 study developed a blood-based risk prediction model by integrating 40 cfDNA methylation markers with six risk factors for distinguishing malignant from benign nodules.

Combining 6 common risk factors with cfDNA methylation markers significantly improved the performance.

36.9% and 25.4% increase in AUC vs. the Mayo Clinic and Brock models ($p < 0.0001$).

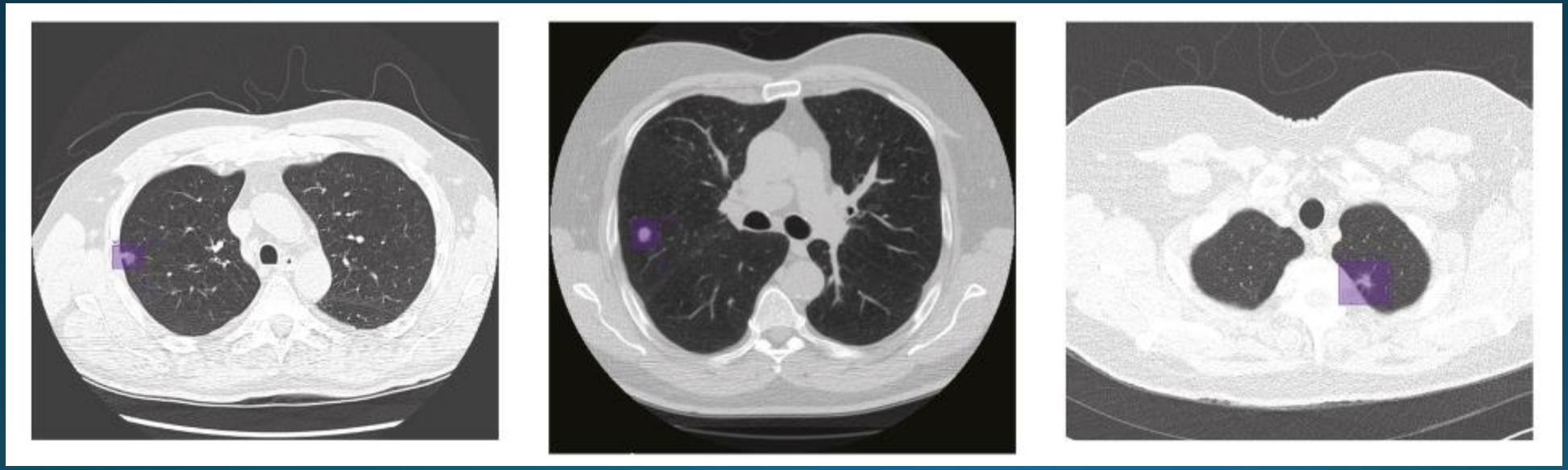


This Technology is currently under clinical investigation.

Liang W, Tao J, Cheng C, Sun H, Ye Z, Wu S, Guo Y, Zhang J, Chen Q, Liu D, Liu L, Tian H, Teng L, Zhong N, Fan JB, He J. A clinically effective model based on cell-free DNA methylation and low-dose CT for risk stratification of pulmonary nodules. Cell Rep Med. 2024 Oct 15;5(10):101750. doi: 10.1016/j.xcrm.2024.101750. Epub 2024 Sep 27. PMID: 39341207; PMCID: PMC11513810.

4. Promise of Deep Learning and AI?

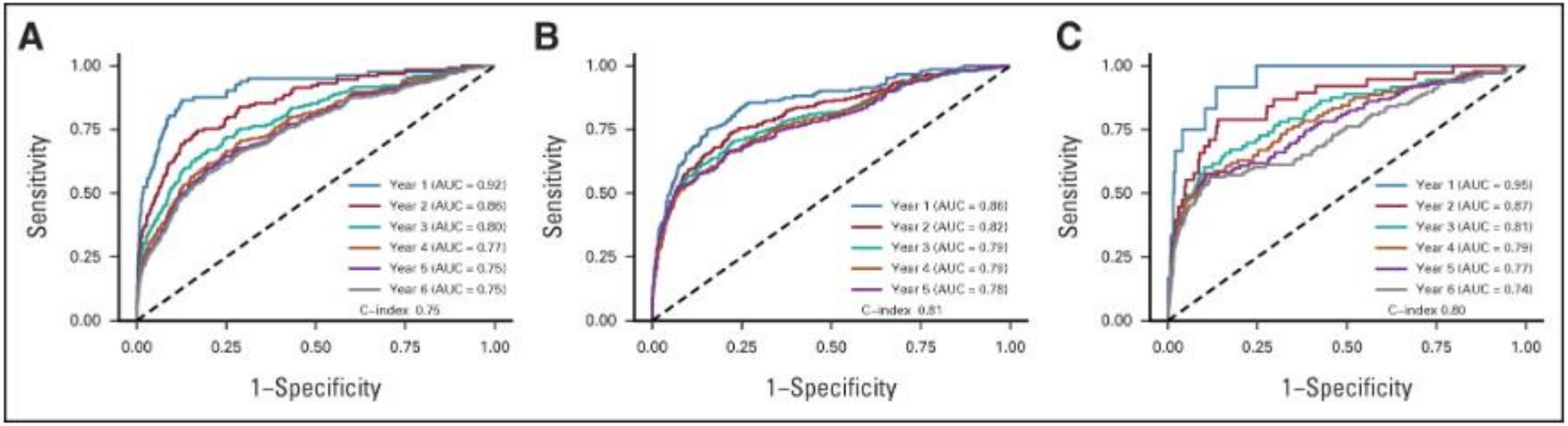
- Deep learning cancer risk model, Sybil, uses a single low-dose chest CT scan to predict lung cancers occurring 1-6 years after a screen



Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Sequist LV, Fintelmann FJ, Barzilay R. Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography. J Clin Oncol. 2023 Apr 20;41(12):2191-2200.

4. Promise of Deep Learning and AI?

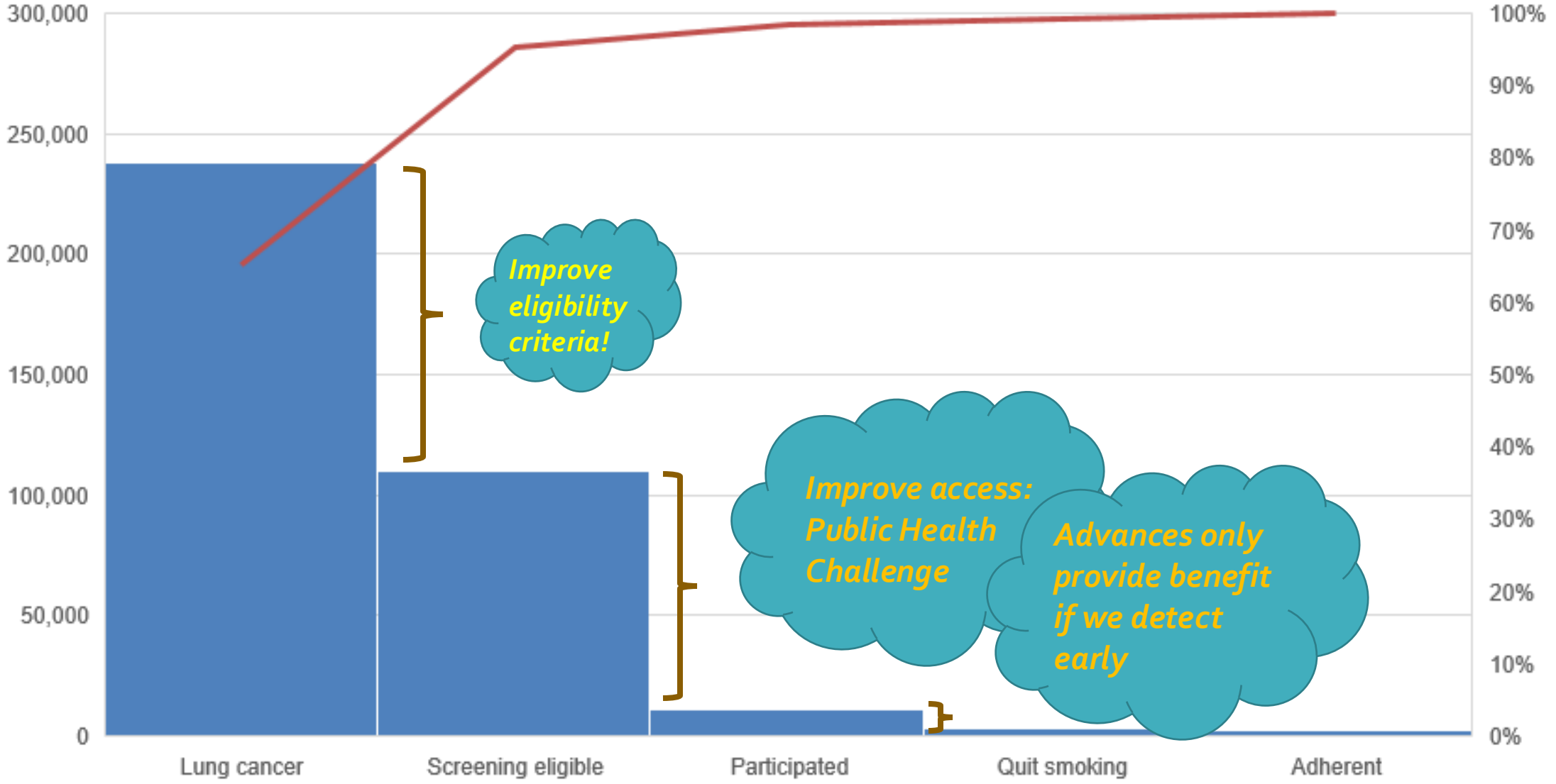
- Sybil can accurately predict an individual's future lung cancer risk from a single LDCT scan to further enable personalized screening, future study is required to understand Sybil's clinical applications.



- Proteomic panels provide promising opportunity.

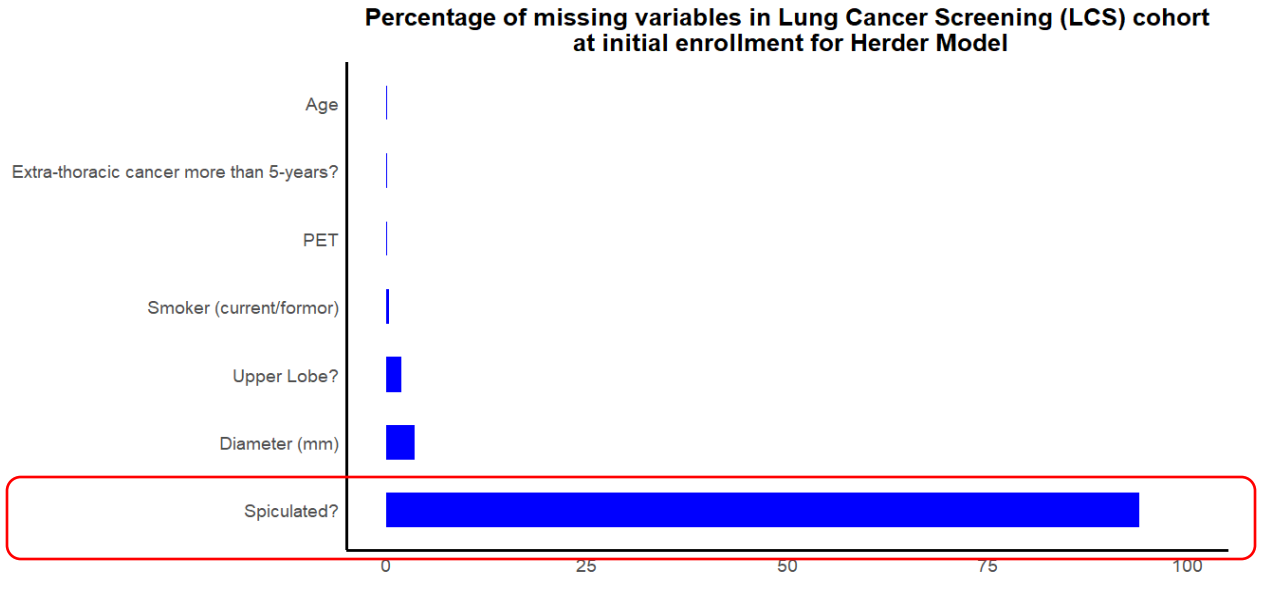
5. What are the broader challenges and implementation barriers?

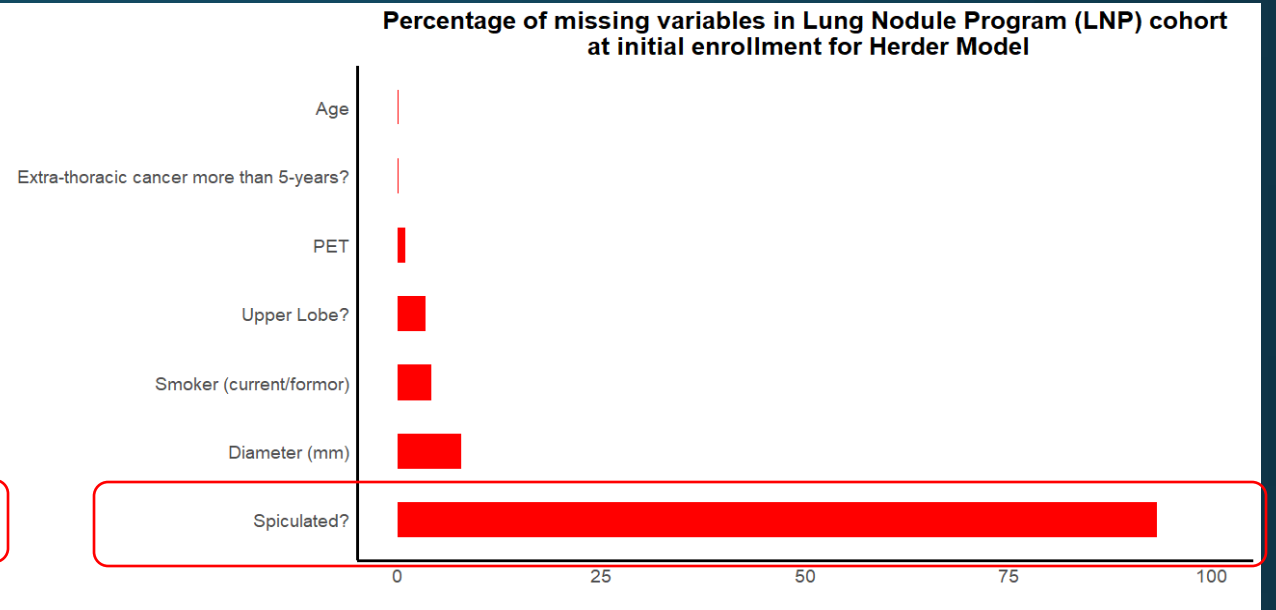
Lung Cancer Screening USA 2023: Population-Level Access and Effectiveness Challenges!

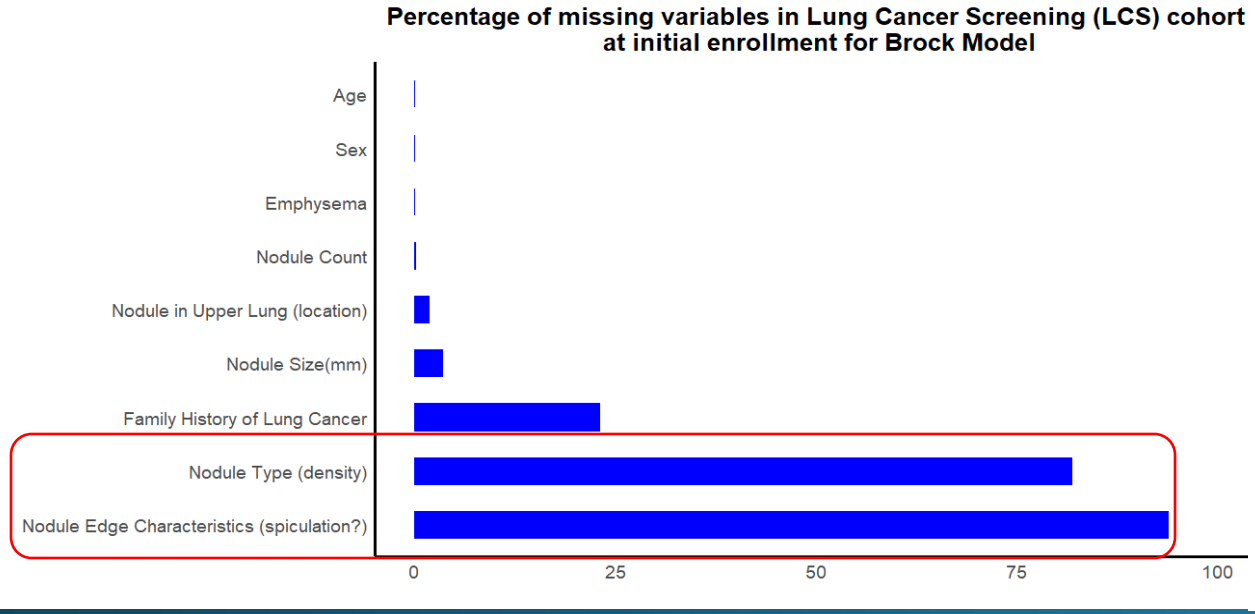


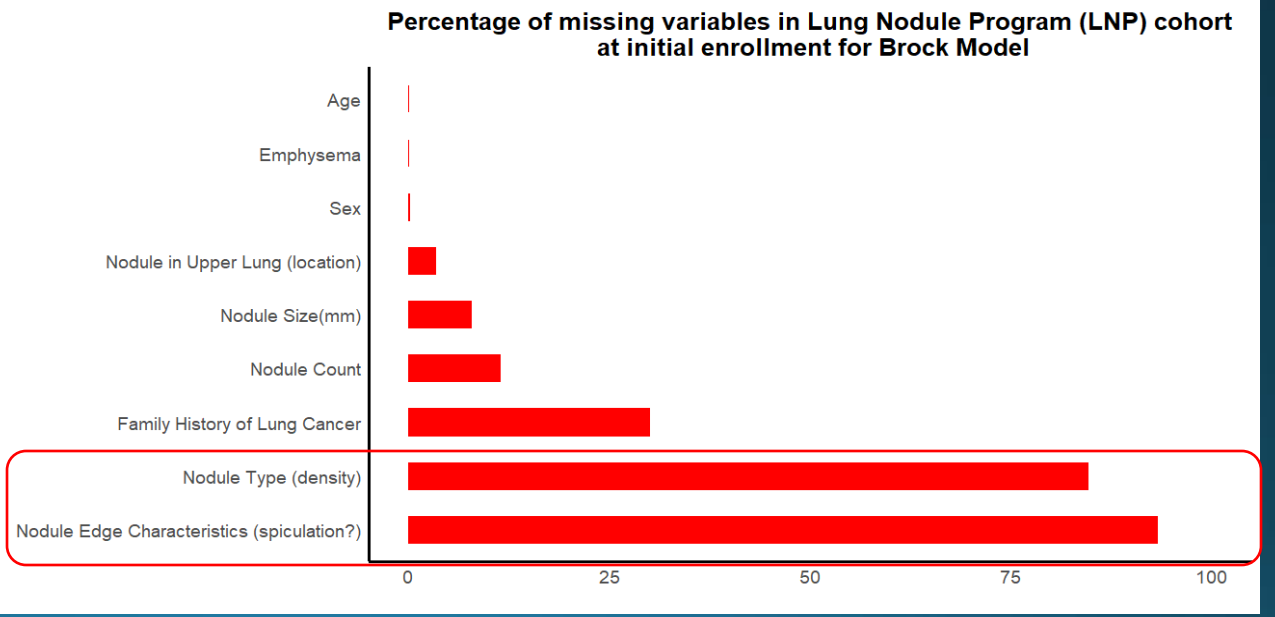
Osarogiagbon, Yang, Sequist. ASCO Educational Book 2023. PMID: 37098234

Missing Variables and the Utility of Lung Cancer and Lung Nodule Risk Calculators in the DELUGE Cohort







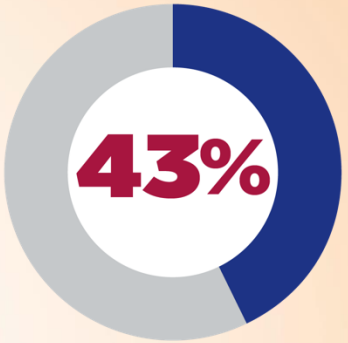


The 2024 IASLC Global Survey on Biomarker Testing

Respondents report that testing rates have improved but continued, substantial barriers exist.

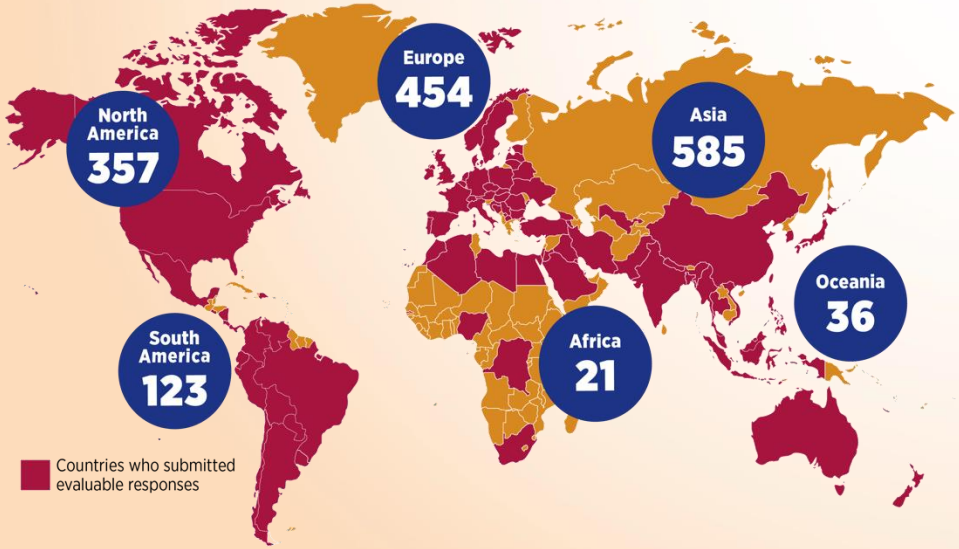
67% estimate more than half of individuals with lung cancer are biomarker tested in their country, up from

39% in the 2018 survey (p-value<0.0001)



Sometimes or often treat patients prior to receiving biomarker results

1,677 responses across 90 countries and 14 disciplines.



The Highest Ranked Barriers

- COST
- TIME
- SAMPLE QUALITY
- ACCESS
- AWARENESS

IASLC PARTNERS FOR THORACIC CANCER CARE

This survey is in partnership with the IASLC Partners for Thoracic Cancer Care.

Smeltzer et al. The 2024 International Association for the Study of Lung Cancer (IASLC) Global Survey on Biomarker Testing. 2024 World Conference on Lung Cancer. OA03..

Take Home Message:

Proteomic and gene expression panels can improve lung cancer risk assessment, show promise for future refinement.

It is important that we optimize implementation and ensure broad access.

Thank you!

Matthew Smeltzer, PhD
Associate Professor of Epidemiology
University of Memphis
msmltzer@memphis.edu
@MattSmeltzer