Existing and Emerging Tests for Cancer Interception

Triparna Sen, PhD

Associate Professor,
Director, Lung Cancer PDX Program,
Department of Oncological Sciences,
Tisch Cancer Institute,
Icahn School of Medicine at Mount Sinai.

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Icahn School of Medicine at Mount Sinai

Lung cancer screening reduces mortality

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The NEW ENGLAND JOURNAL of MEDICINE

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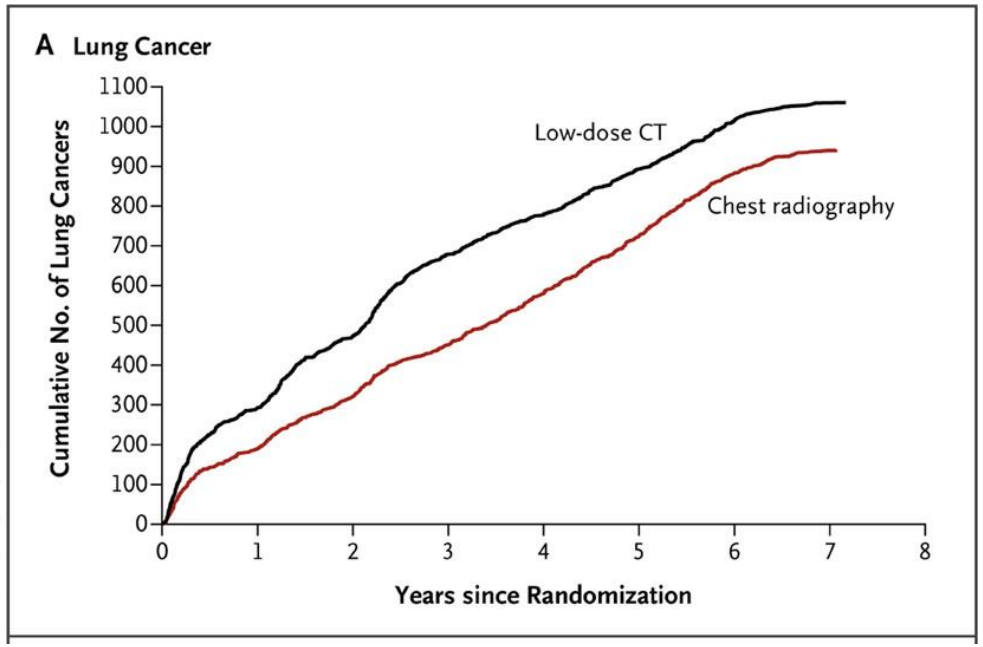
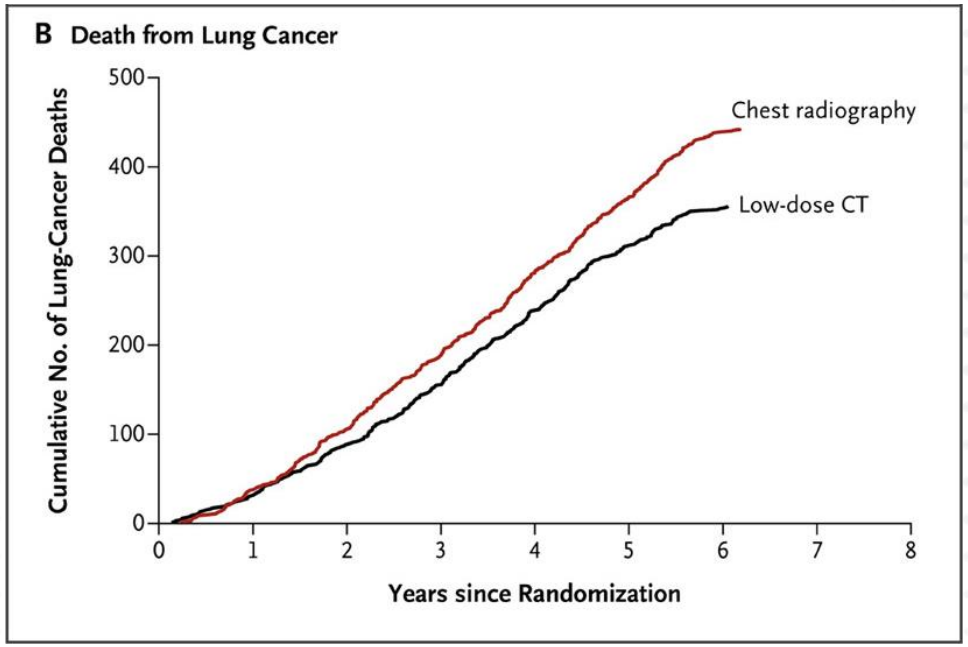
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*





Reduce 20% lung cancer-related motility, based on 53439 high-risk individuals RCT and 6.5 years follow up.

Challenges on early lung cancer diagnosis

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- Millions of pulmonary nodules are detected annually due to high sensitivity.
  - LDCT/CT: ∽10% at Stage 0 and ∽ 75% at stage I
- High overtreatment in lung cancer only based on CT imaging: around 10-40% overtreatment.
- Clinical risk prediction models (Mayo, Brock, AV) : 60-90% accuracy.
- Accurate and cost-effective tools are needed to assist nodule diagnosis and management.
- DNA methylation biomarkers improved specificity and accuracy in distinguishing malignant pulmonary nodules from benign nodules.

Overview

- Cell-Free DNA Methylation for Risk Stratification of Pulmonary Nodules.
- Circulating T cell receptor repertoire analysis for early detection.
- Blood microRNA test in lung cancer screening
- AI in lung cancer screening

An Effective Multimodel Based on Cell-Free DNA Methylation for Risk Stratification of Pulmonary Nodules

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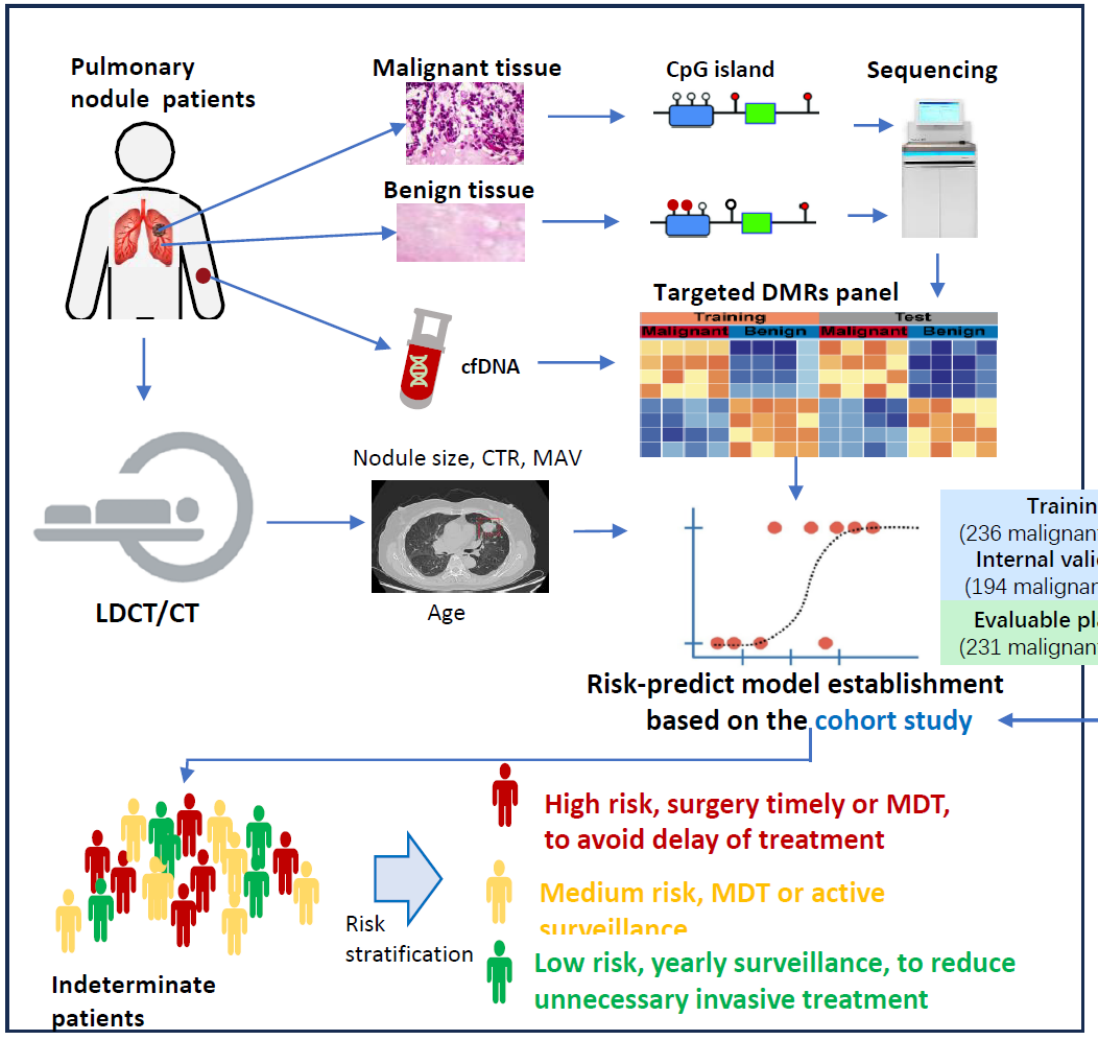
Study Design

- **Discovery of lung cancer-specific DNA methylation biomarkers**: genome-wide sequencing on 52 malignant vs 16 adjacent and normal 60 benign lung tissues.
- **Construction of a target methylation panel for malignant nodule identification using blood test**: using narrowed down Differentially Methylated Regions (DMRs)
- **Establishment and validation of a cfDNA methylation model for pulmonary nodule risk stratification:** in two prospective-collection, multi-center, observation clinical studies. (AUC, sensitivity, specificity, accuracy)
- **Improved performance by combining with clinical and 5 CT imaging features:** age, long/short diameter, area, CTR, MAV.



Liang et al., WCLC 2024

Meth-Biomarker selection for panel construction

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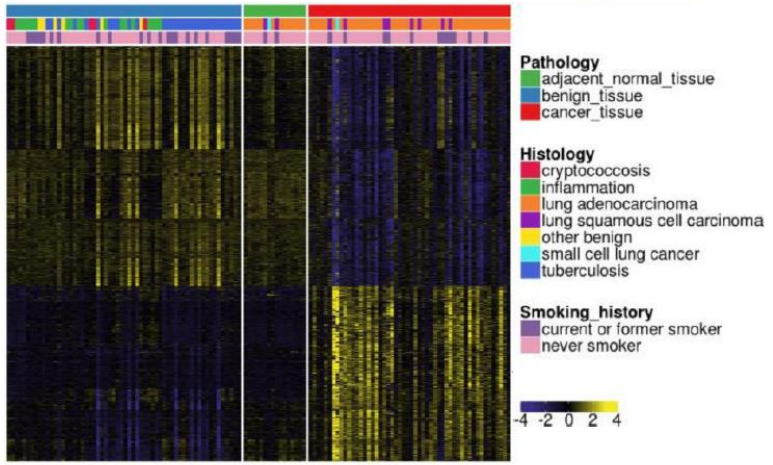
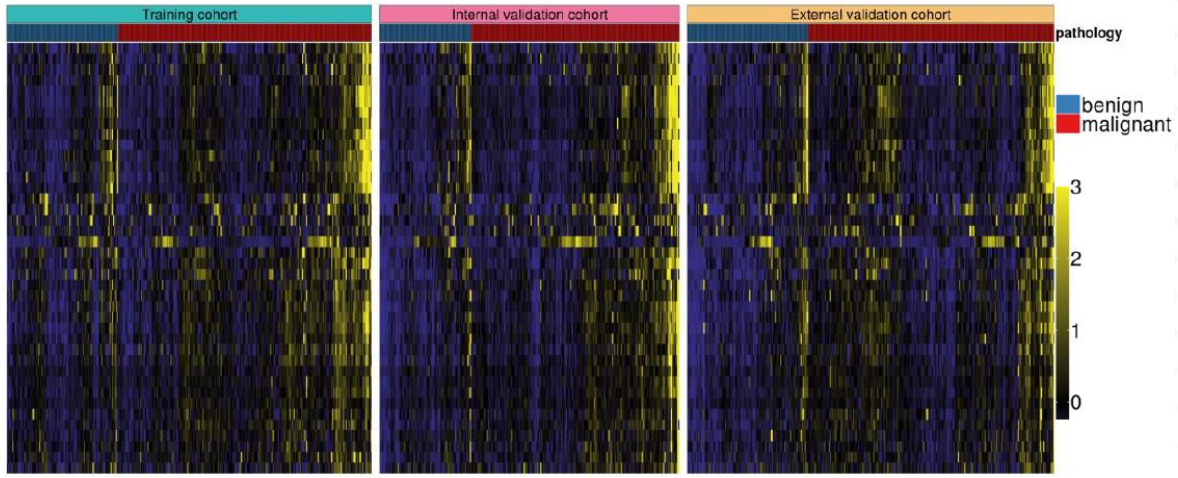
- **Screening of lung cancer-specific DNA methylation biomarkers:** genome-wide sequencing on 52 malignant vs 16 adjacent and normal 60 benign lung tissues **(A)**. (methylation difference ≥ 0.05, p <0.01)
- **Construction of a target methylation panel for malignant nodule identification using blood test**: containing 263 DMRs → narrowed down to 40 DRMs by multiple steps.
- **40-gene methylation marker signals in plasma samples**: in the training cohort, internal validation cohort and external validation cohort **(B)**.

A. DMRs of genome-wide Meth-sequencing on lung tissues



B. DMRs of 40-gene targeted Meth-sequencing on plasma cfDNA in three cohorts



Liang et al., WCLC 2024

Multimodel for malignant identification

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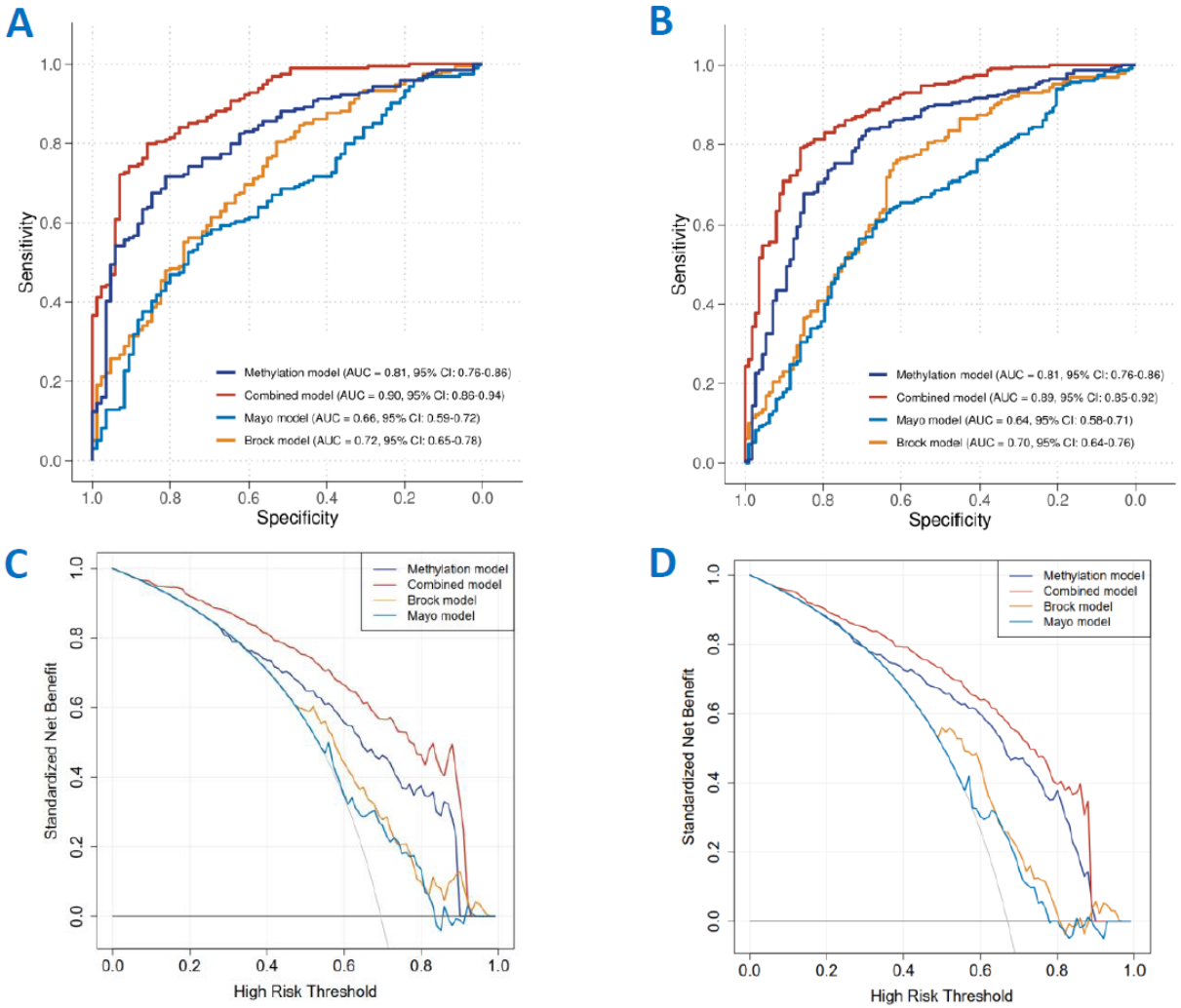
- **Methylation-only model:** (A,B)
  AUC=0.81 vs Myao Clinic (0.66) and Brock (0.72)
  Sensitivity=0.89 vs Myao Clinic (0.69) and Brock (0.81) when specificity fixed at 0.51.
  Accuracy=0.77 vs Myao Clinic (0.63) and Brock (0.72)

- **Combined model:** (A,B)
  AUC=0.89-0.90, with 0.08-0.09 increased.
  Sensitivity=0.95-0.97, with 0.06-0.07 increased.
  Accuracy=0.80-0.83, with 0.03-0.05 increased.
  PPV=0.80-0.82
  NPV=0.99 (10% prevelance)

- **Decision curve analysis (DCA): with a standardized net benefit of 79.1% from the combined model:** it means correctly identify approximately 79 individuals with malignant nodules from 100 people with lung cancer, if to consider an invasive procedure for a patient with a risk score more than the threshold of 0.40. (C, D)

Internal validation cohort

External validation cohort



Liang et al., WCLC 2024

Two-threshold strategy for accurate risk stratification of pulmonary nodules

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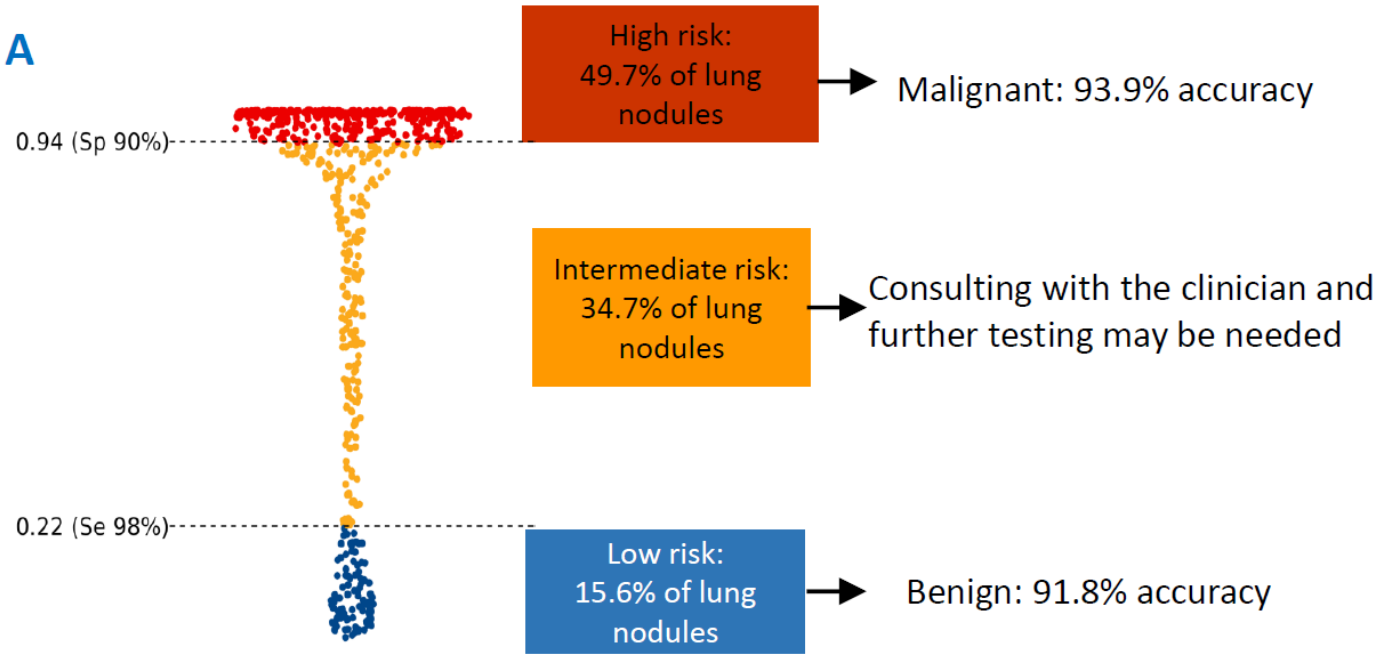
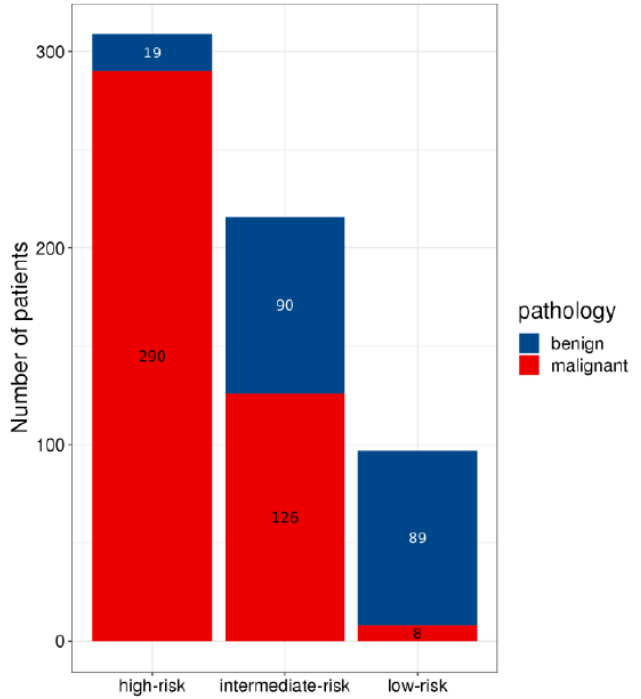
- **Two cutoffs simultaneously to classify pulmonary nodules into low-risk (risk score <0.22), intermediate-risk (risk score from ≥0.22 to <0.94), and high-risk (risk score ≥0.94) groups.** (A)
- **High risk nodules**: 49.7% of total; with 93.9% accuracy
  Low risk nodule: 15.6% of total; with 91.8% accuracy
  Intermediate risk: 34.7% of total; active follow up

Reduce unnecessary invasive surgeries	**90.4%** (89+90/198)
Malignant nodules misclassified and falls into surveillance	1.9% (8/424)
Benign nodules misclassified and undergone invasive surgeries	9.6% (19/198)

A



B



Liang et al., WCLC 2024

Overview

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Liquid biopsy is a promising complementary approach for lung cancer screening, but sensitivity is limited

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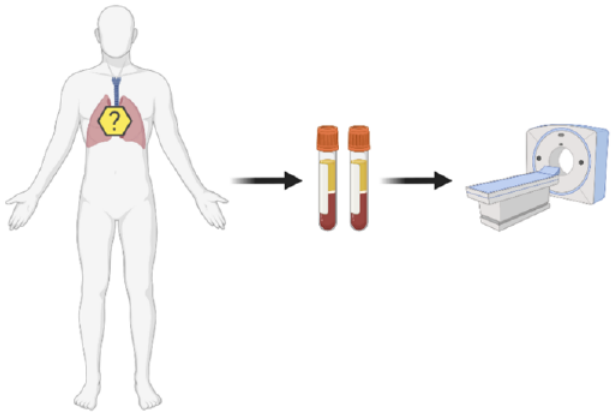
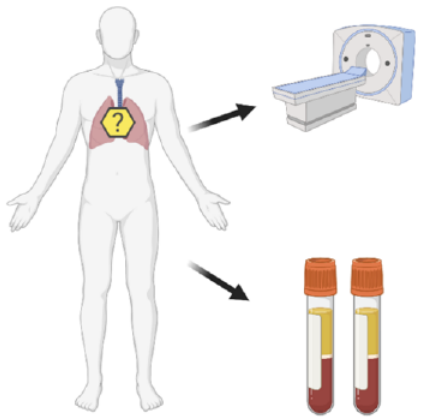
1 Possibility to increase population of individuals eligible for screening

Nearly half of lung cancer cases are still ineligible for screening

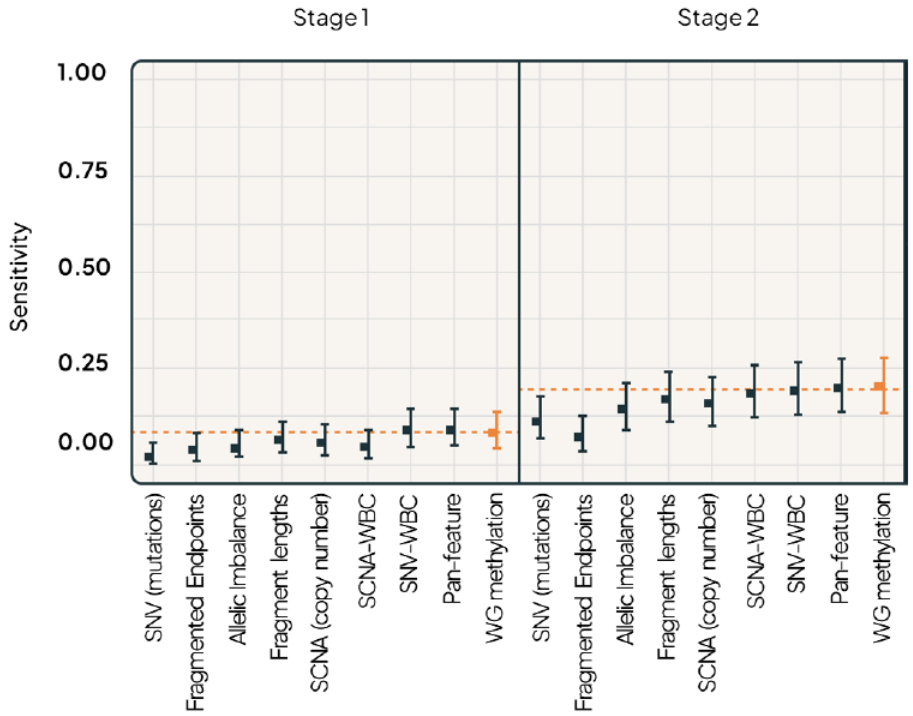


2 An alternative for those unable or unwilling to undergo regular LDCT.

14.5 million Americans now eligible for annual screening, but <10% get screened



But low sensitivity of circulating tumor DNA for early-stage cancer limits liquid biopsy application to early detection



Sources: Osarogiagbon, et al., JCO, 2022; Henderson, et al., JAMA 2021; Tanner, et al., Chest 2015; Gould, et al., AJRCCM 2015; Jamshidi, et al., Cancer Cell 2022

Montuenga, et al., WCLC 2024

Improving early detection liquid biopsy by adding testing of the anti-tumor T cell response

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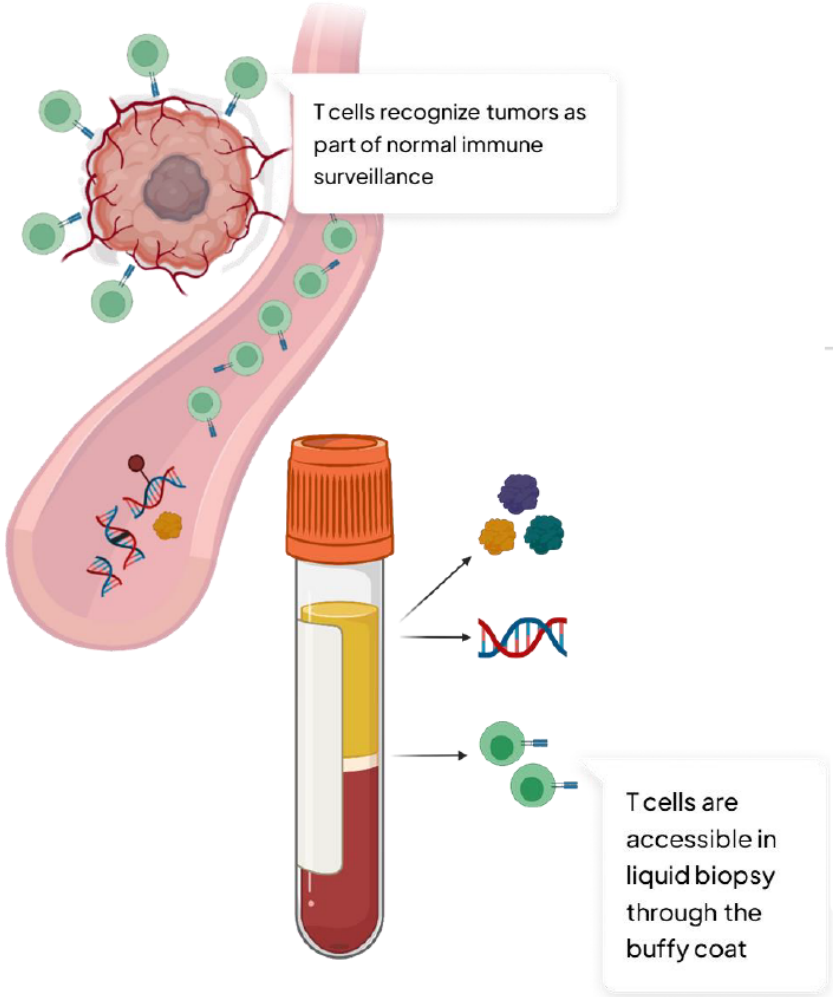
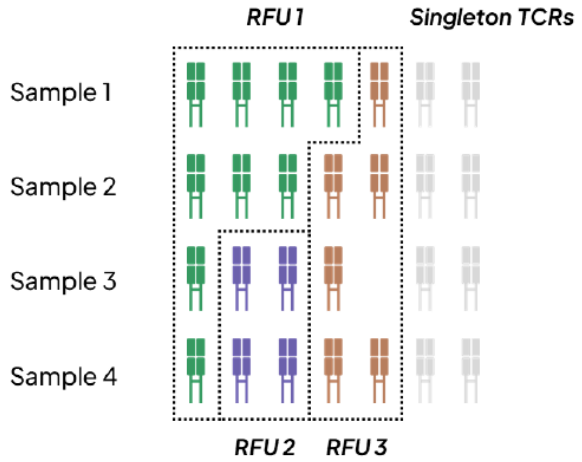
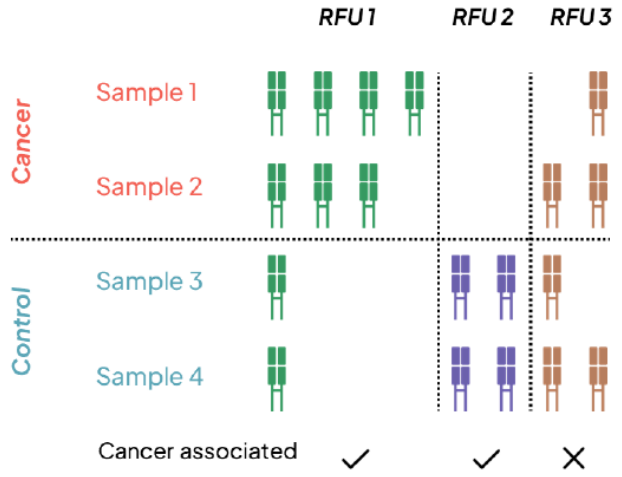


1. Sequence circulating TCRs and group TCRs with similar sequence into repertoire functional units (RFUs) with putative shared antigen specificity



2. Identify TCR RFUs associated with cancer case / control status and use these TCR RFUs in a machine learning model to detect presence of cancer via liquid biopsy



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Lung cancer case & control blood sample cohort to discover TCR RFUs (N = 1071 subjects)

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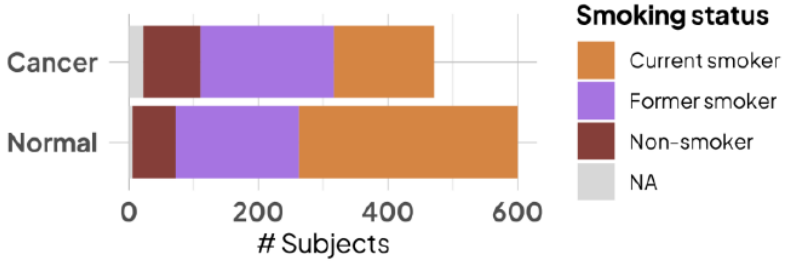
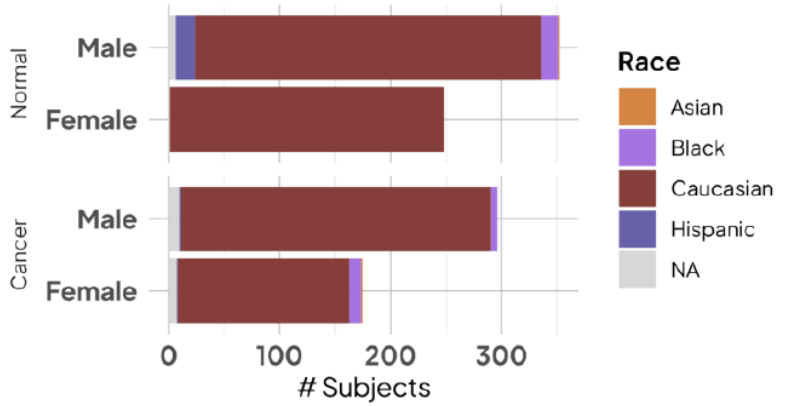
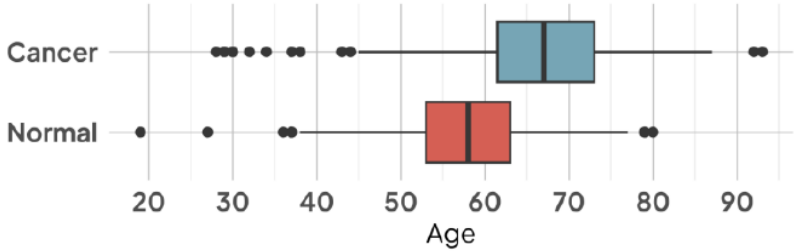
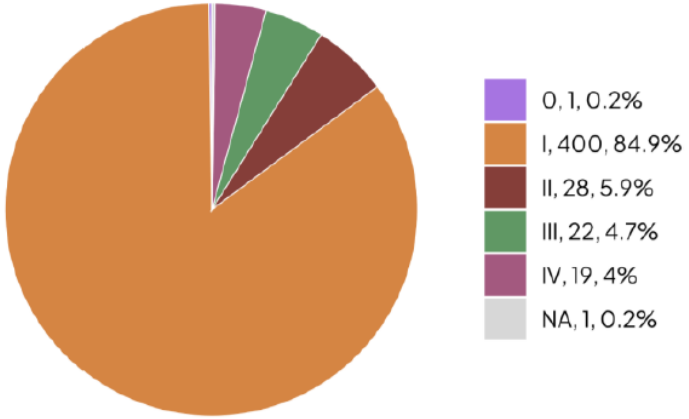
Subject demographics



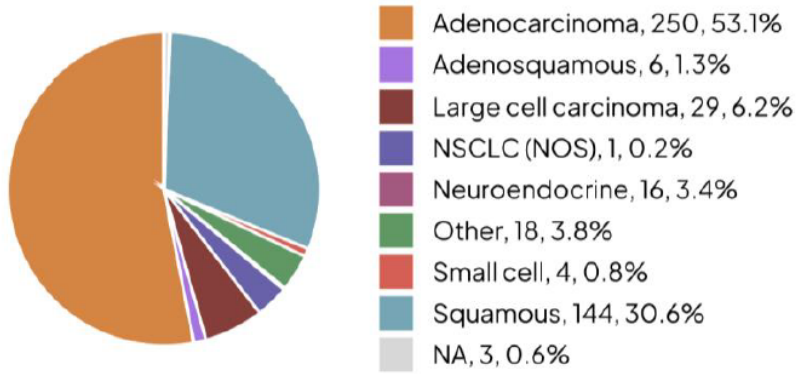




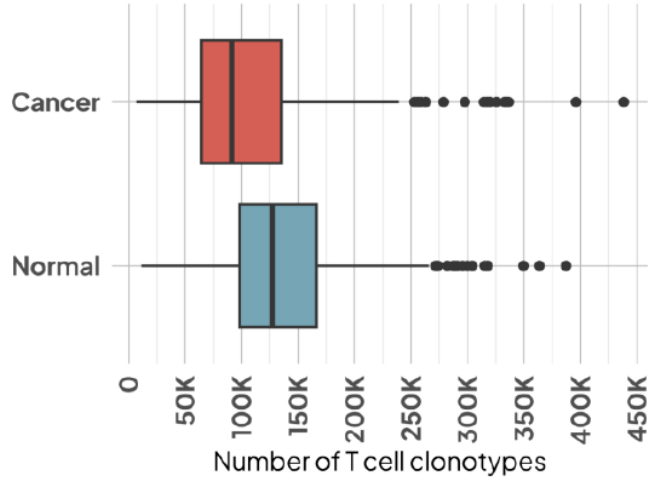
Cancer stage



Cancer histology



Clonotype count distribution across subjects: 75M total unique clonotypes



Blood was collected in Streck Cell-Free DNA BCT® or EDTA tubes. TCR beta chain sequencing was performed on a target 8ug of input genomic DNA using a multiplex PCR UMI-based NGS assay covering 58 V and 13 J genes

Montuenga, et al., WCLC 2024

Identification of TCR RFUs (n=372) that can be used to detect lung cancer through liquid biopsy

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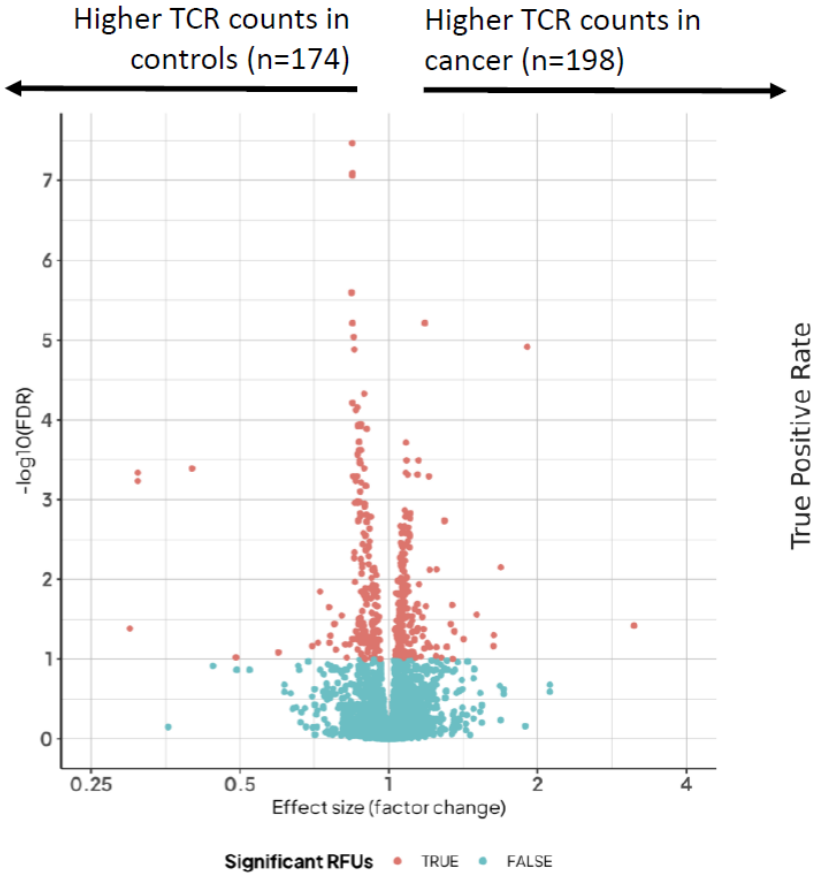
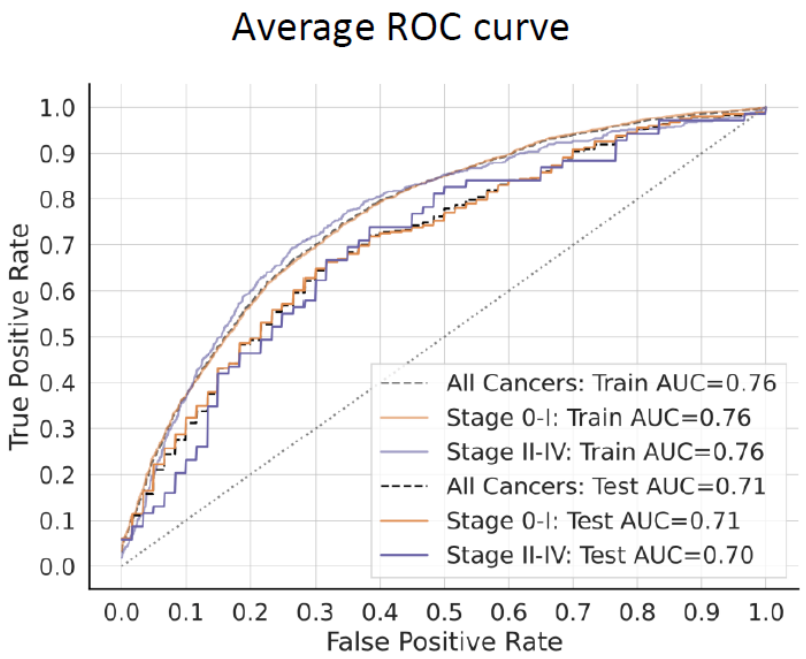
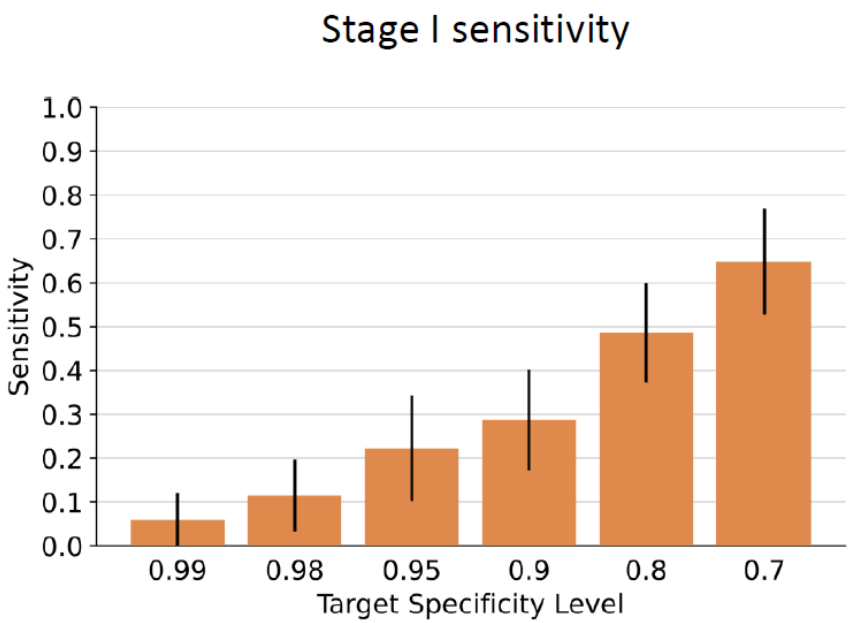


p-values and FDRs from likelihood ratio test of negative binomial model for RFU TCR counts +/- cancer status, adjusting for age, gender, race as covariates and filtering for recurrent RFUs





Data from SVM model, linear kernel, with bagging. Showing average 10-fold cross-validation (CV) performance of full RFU discovery process inclusive of nearest neighbor graph construction and clustering.

Montuenga, et al., WCLC 2024

TCR RFU cancer signal is orthogonal to existing analytes and improves sensitivity for Stage I lung cancer

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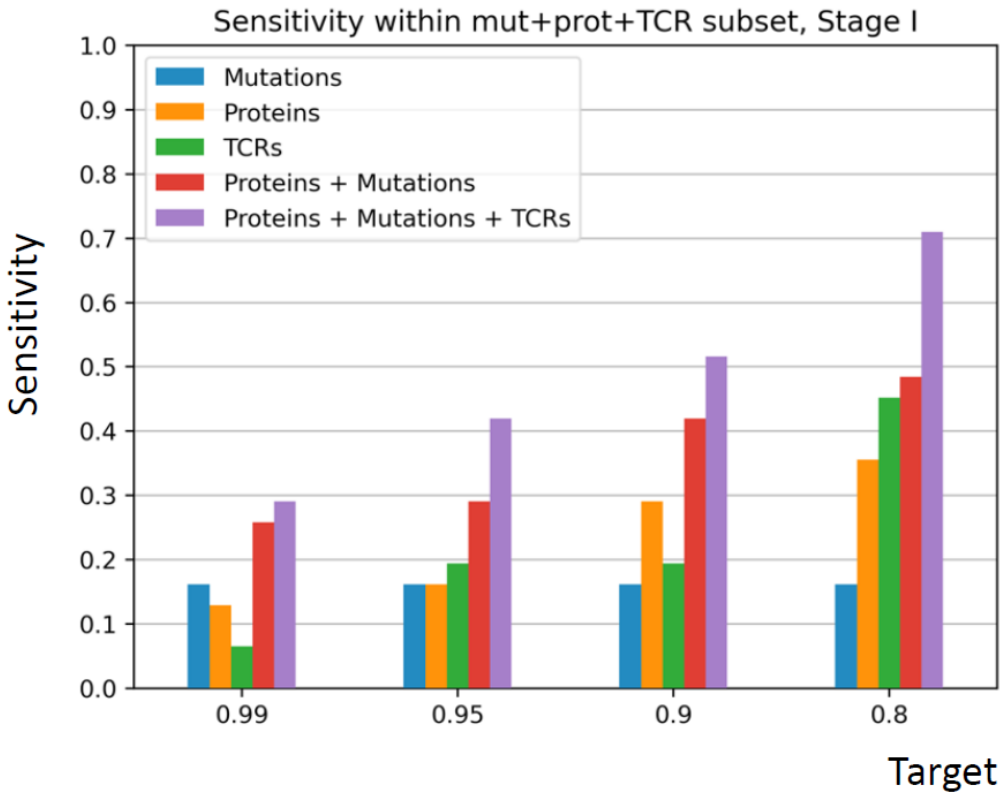

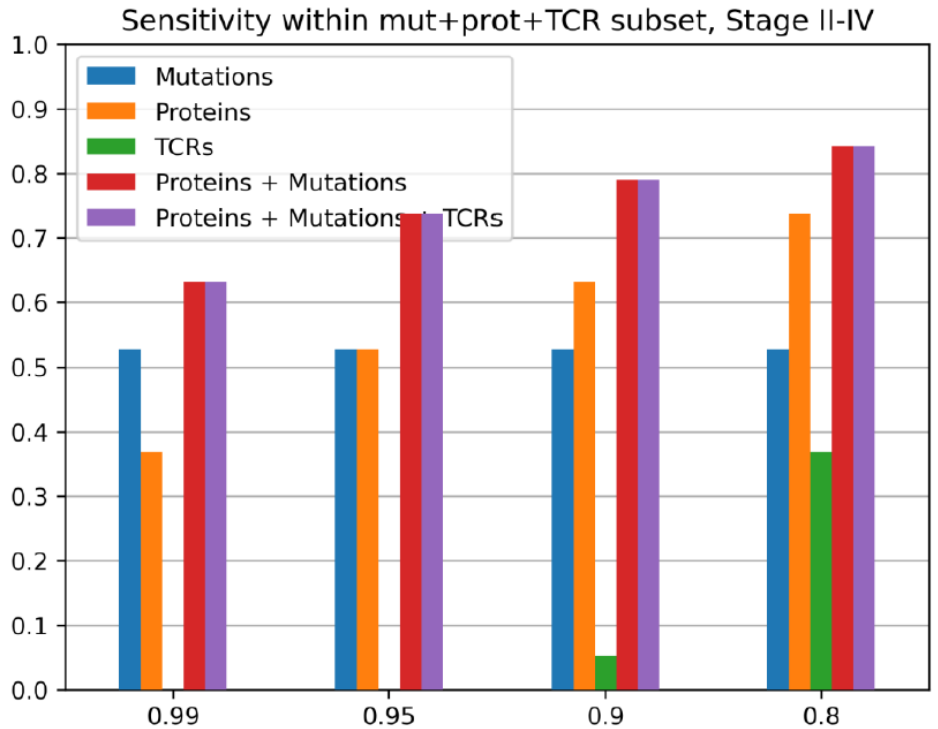

Stage	N
I	31
II	5
III	8
IV	6
No cancer	36
Total N	86

Notes: Per-sample per-analyte calls for the N=86 subjects with all 3 analytes are from CV test folds from individual analyte models (N=1071 subjects with TCR, N=112 with mutations, N=235 with protein data) at the target specificity or higher within each fold

Comparison of lung cancer status prediction using TCR RFUs to ctDNA (237 mutation hotspots in 154 cancer driver genes) and 17lung cancer-related protein biomarkers, including CEA, KRT19, IL6, WFDC2, TGFA

Montuenga, et al., WCLC 2024

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- AI in lung cancer screening.

The microRNA signature classifier (MSC)

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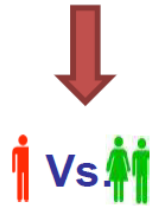
TRAINING SET

Pilot study: 1035 high risk individuals

38 LC within 5 years



Vs.

Plasma collection

microRNA profiling

Signature generation

MSC	Risk level
Positive	High
	Intermediate
Negative	Low

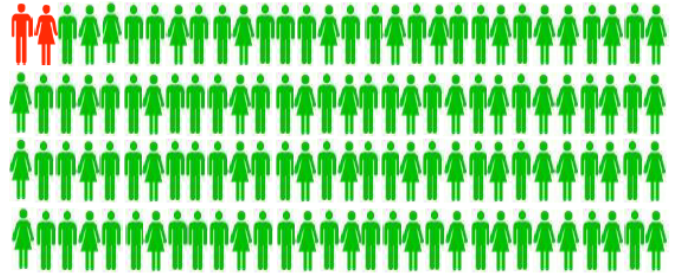
Ratios between 24 microRNAs

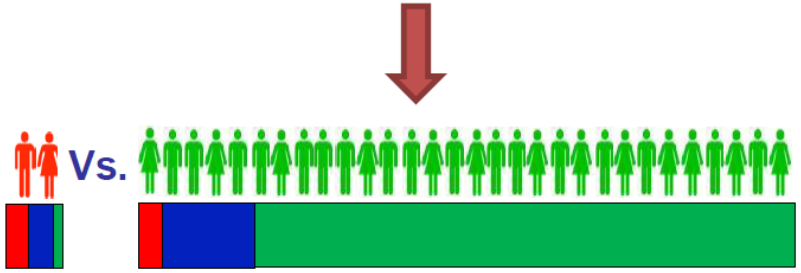
Boeri et al. PNAS, 2011

VALIDATION SET

MILD: 4099 high risk individuals

85 LC within 5 years





Vs.

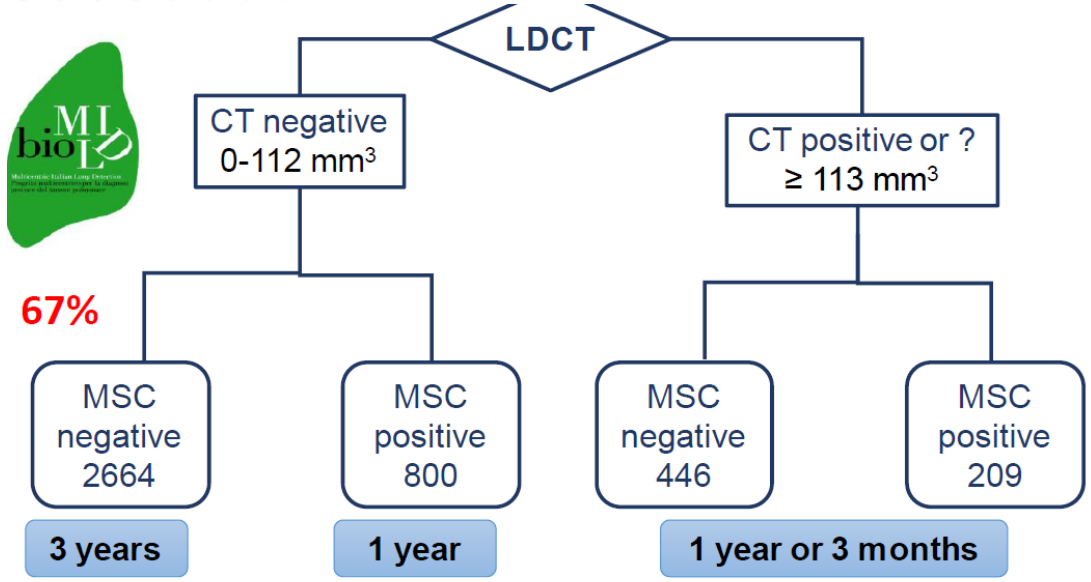
87% Sensitivity

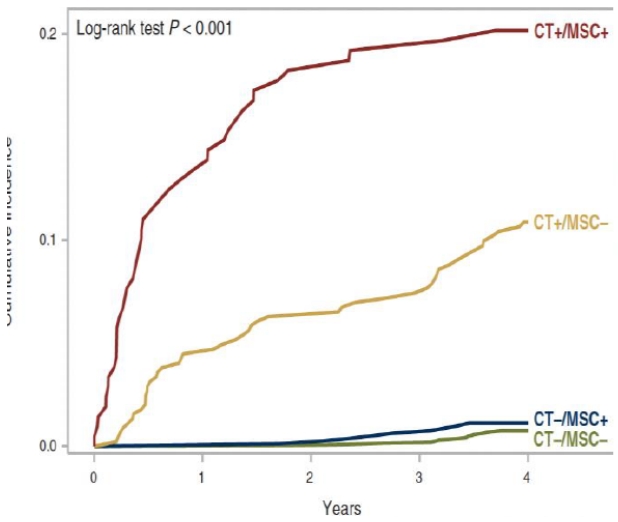
81% Specificity

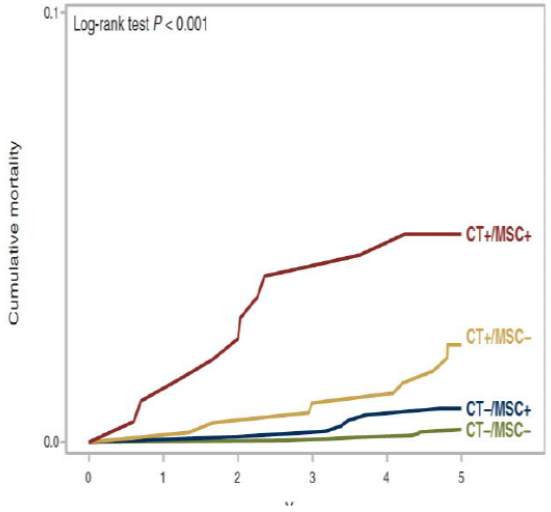
Sozzi et al. JCO, 2014

Sozzi, et al., 2024

The BioMILD screening trial



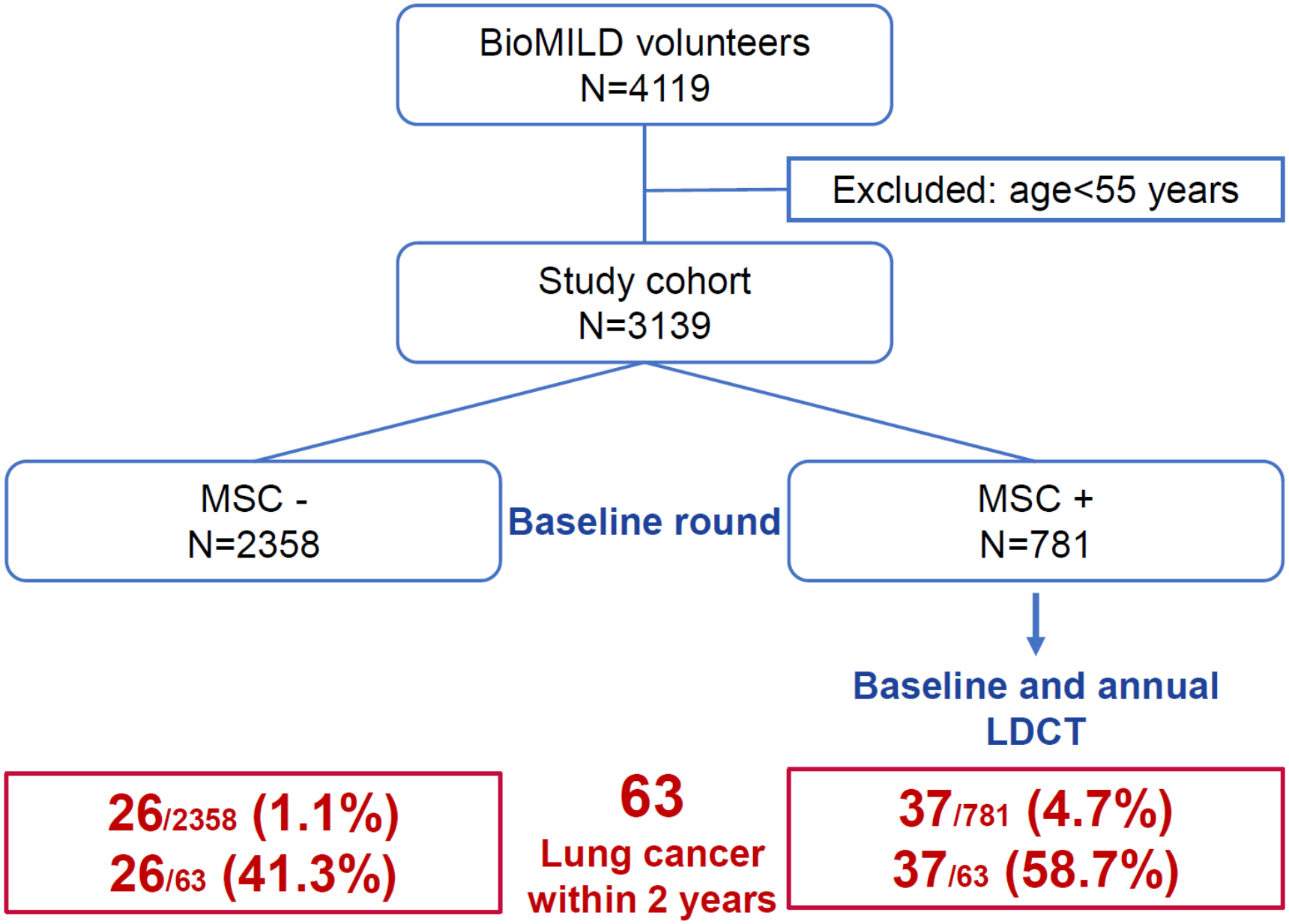




- **Baseline** LDCT and blood microRNAs profile (MSC) define **individual lung cancer risk** profiles.
- Targeted LDCT intervals reduce **unnecessary repeat LDCT** without **detrimental effect** (stage I LC, resection rates, interval cancers)
- MSC risk test shows a **major added value for CT indeterminate/positive** participants

Saving >30% CT exams in 3 years

Pastorino U. et al., Annals of Oncology 2022



Sozzi, et al., WCLC 2024

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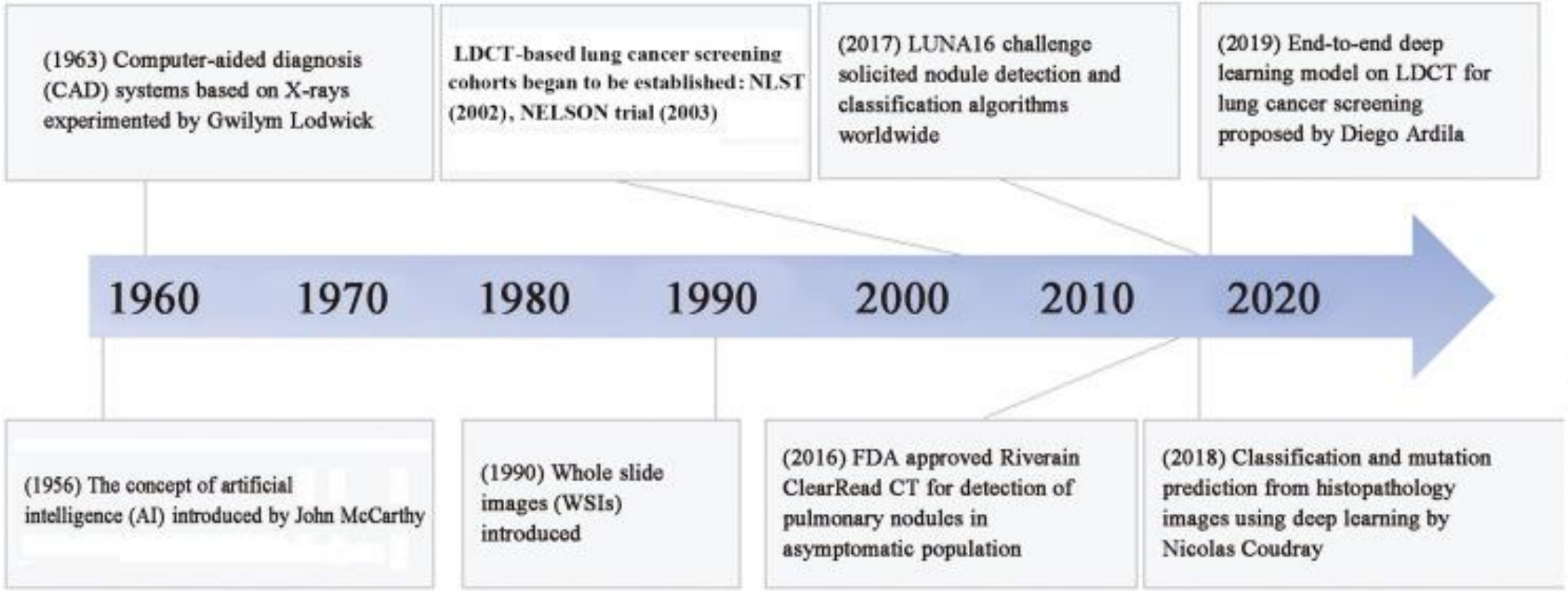
Milestone of AI in lung cancer



- There is growing interest in using artificial intelligence (AI) decision-support tools to enhance lung cancer risk prediction.
- However, their performance needs to be compared with existing lung cancer risk prediction tools using cohorts with adequate follow-up and known outcomes before prospective evaluation in clinical settings

Shao, et al., 2023

Comparison of Sybil with Brock and PLCOm2012 Models among Screening Participants with Positive and Negative Baseline Screens

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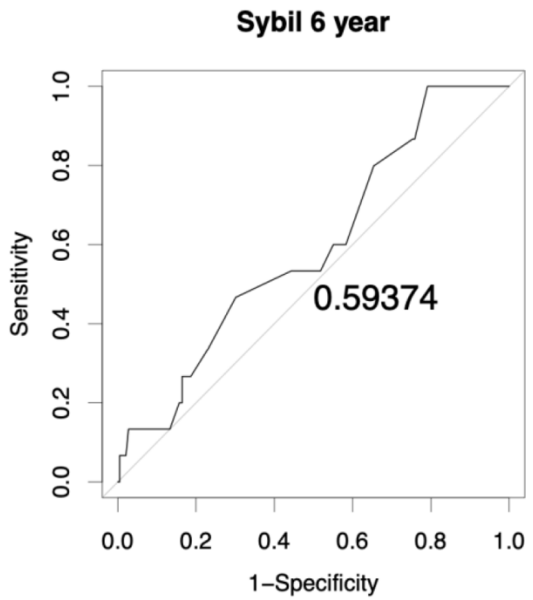
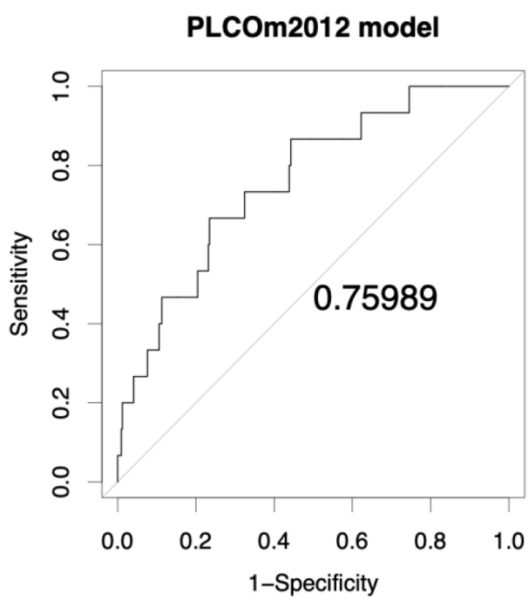
Baseline LDCTs from the International Lung Screening Trial (ILST) Vancouver (N=2121) and the Pan-Canadian Early Detection of Lung Cancer Study (PanCan, N=2192) were analyzed with Sybil

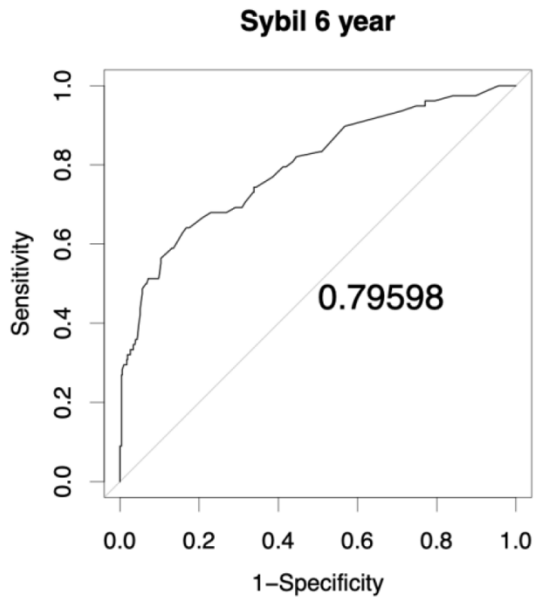
ILST individuals without nodules or with nodules with cancer prob<1.5%

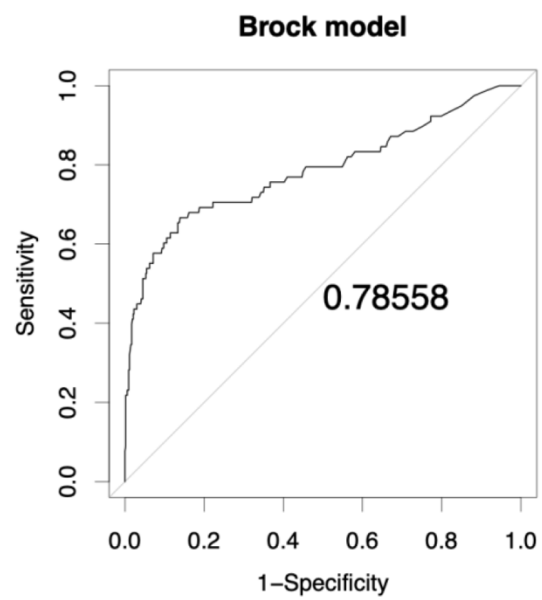




For individuals with negative screens (having no nodule with Brock probability <1.5%), PLCOm2012 had better risk prediction than Sybil

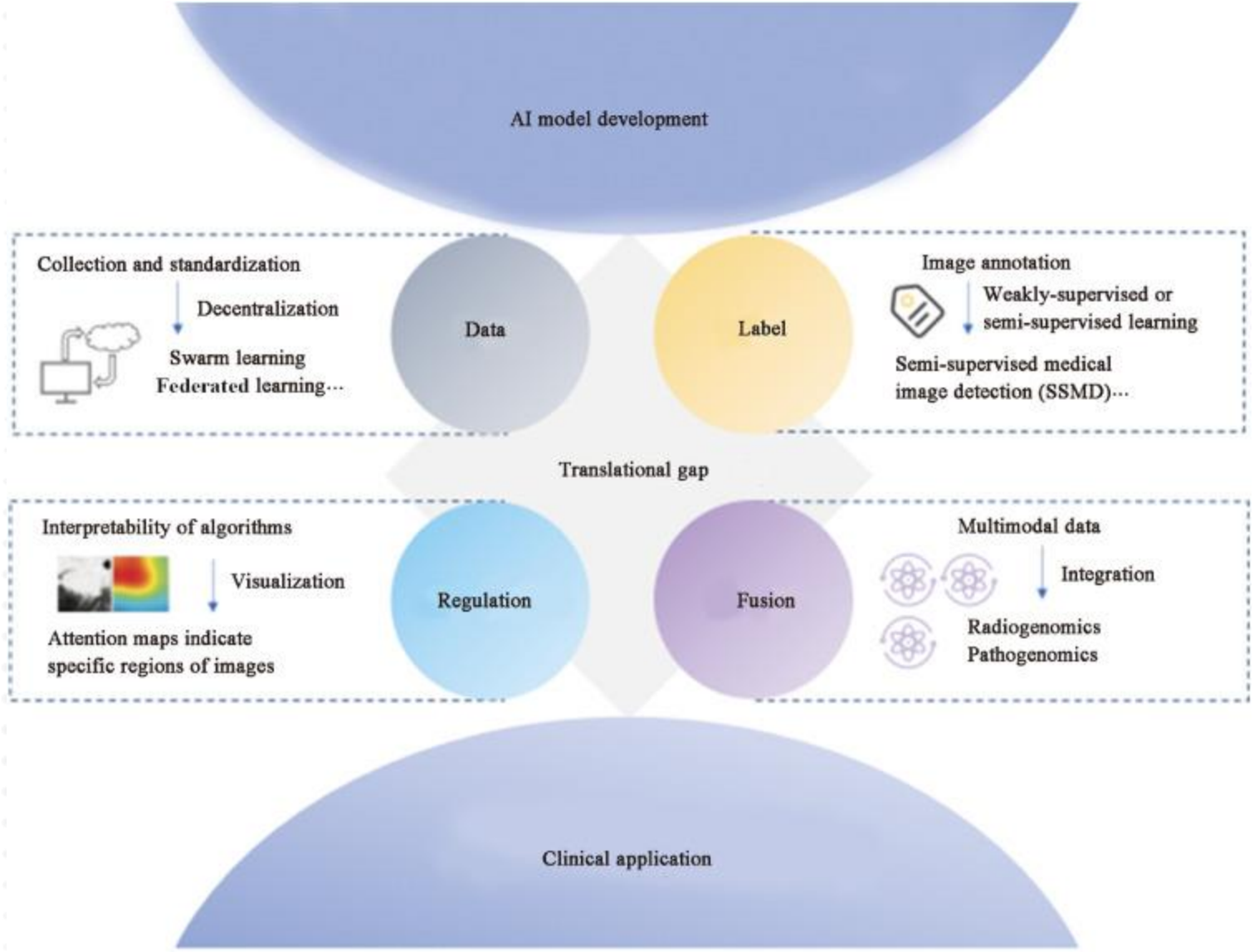
ILST individuals with nodules with cancer prob>=1.5%





Similar risk prediction between Sybil and the “Brock model” for those with positive screens (having at least one nodule with Brock probability >1.5%)

Existing translational gap from AI models to clinical application



Shao, et al., 2023

Acknowledgments

Twitter: @triparnasen
Email: triparna.sen@mssm.edu
Website:
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Patients and their families!