Lung Cancer UPDATES
WCLC HIGHLIGHTS
06 - 09 SEPTIEMBRE 2025
Barcelona, Spain

Iniciativa científica de:
GECP lung cancer research

Biomarcadores, factores de riesgo y screening

M. Lázaro

Hospital Álvaro Cunqueiro de Vigo

COIs

Consultant or Advisory Role: BMS, MSD, Takeda, Roche, Pfizer, Roche, Ipsen, Astra-Zéneca,

Boehringer, Bayer, Janssen, Recordati

Speaking: GSK, Roche, Ipsen, Lilly, Astellas, Janssen, Novartis, Boehringer, Eisai, Sanofi

Grant or travel support: MSD, Ipsen, Roche, Janssen, Pfizer, Astellas, Takeda

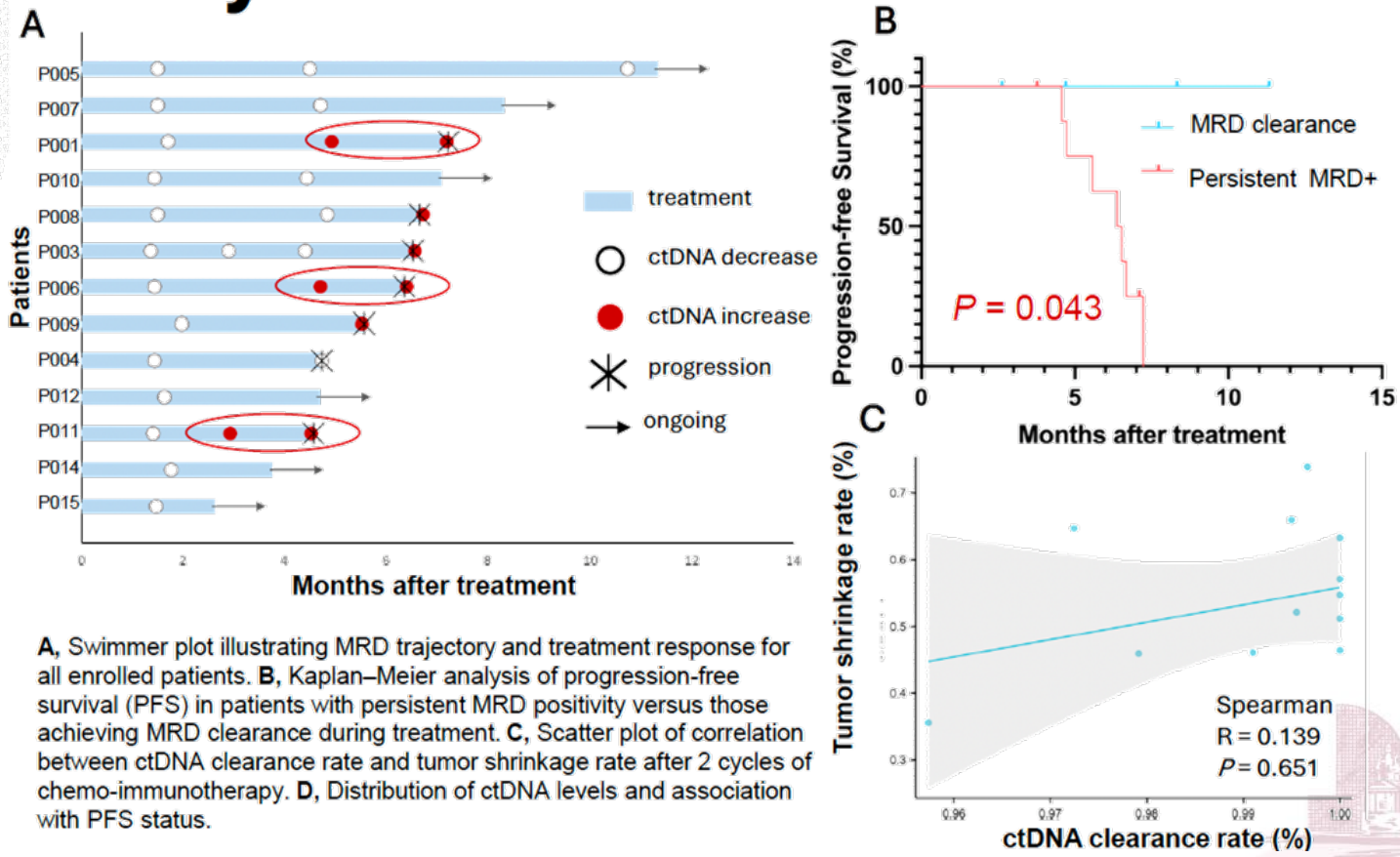
Participation in clinical trials: Merck, Astellas, Pfizer, Ipsen, Roche, AZ, Mirati, PharmaMar, Gilead, Regeneron, Summit Ther

Biomarcadores

MRD en la monitorización en pacientes tratados con serplulimab + quimioterapia en 1L

Key results

ORR: 100% DCR: 100% (13/13)



	N	mPFS, mo (95%CI)
MRD clearance	4/13	NA
Persistent MRD+	9/13	6.26 (5.49-NA)

A, Swimmer plot illustrating MRD trajectory and treatment response for all enrolled patients. **B,** Kaplan–Meier analysis of progression-free survival (PFS) in patients with persistent MRD positivity versus those achieving MRD clearance during treatment. **C,** Scatter plot of correlation between ctDNA clearance rate and tumor shrinkage rate after 2 cycles of chemo-immunotherapy. **D,** Distribution of ctDNA levels and association with PFS status.

Xu, IASCLC 2025

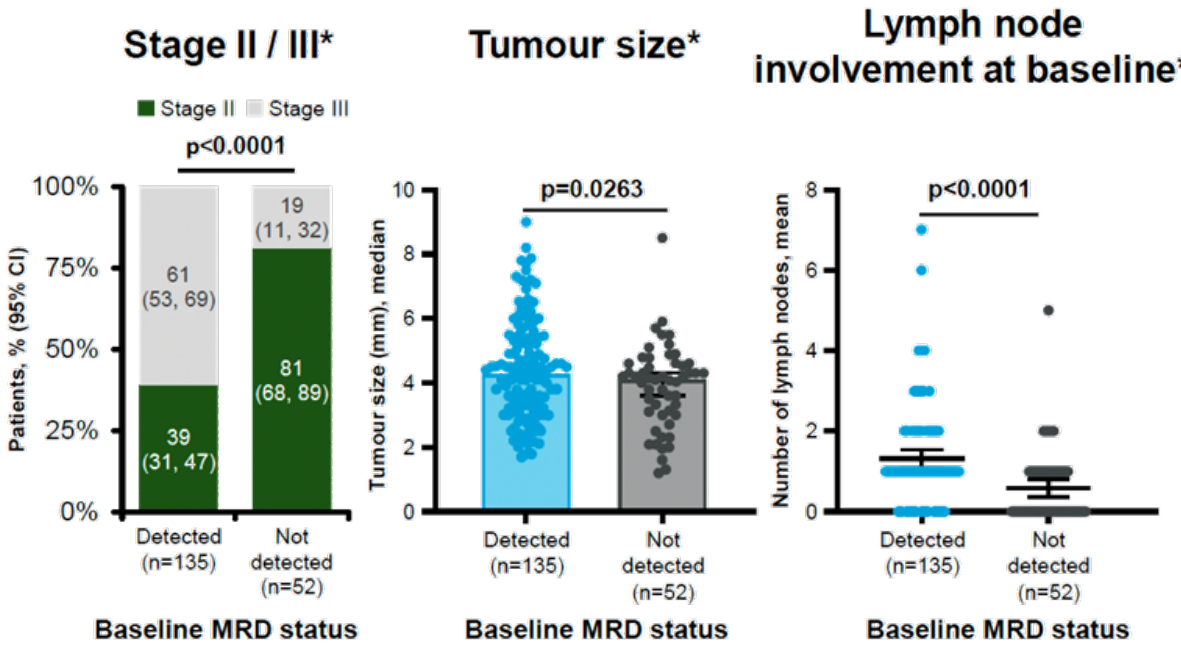
MRD en la monitorización en pacientes tratados con serplulimab + quimioterapia en 1L

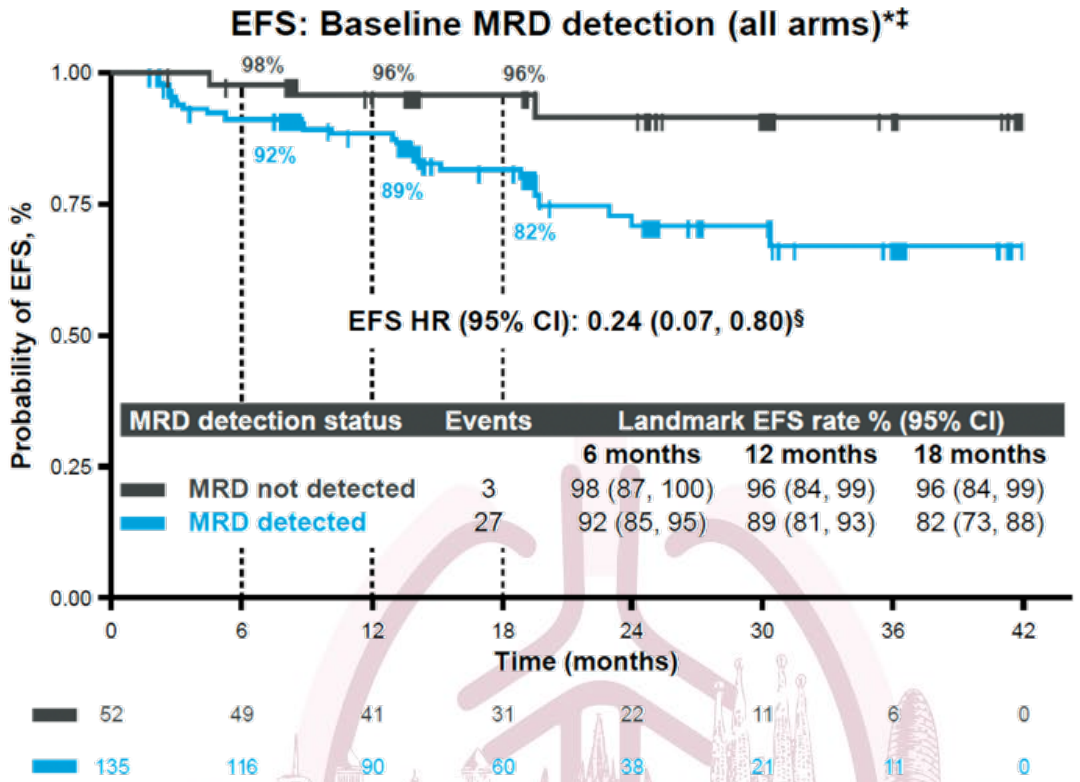
Take home message

- ctDNA-based MRD detection represents a promising biomarker for predicting prognosis in ES-SCLC. MRD clearance during treatment predicts better PFS.
- ctDNA monitoring is more sensitive than conventional imaging for detecting progression, identifying molecular signs of disease progression months earlier.
- These preliminary findings, based on a small cohort, highlight the need for further validation with expanded data.

Xu, IASCLC 2025

MRD en el NeoADAURA





Other patient characteristics (EGFR mutation type, race, age, sex, smoking, WHO PS, surgery) were similar between the baseline MRD detected vs not detected groups†

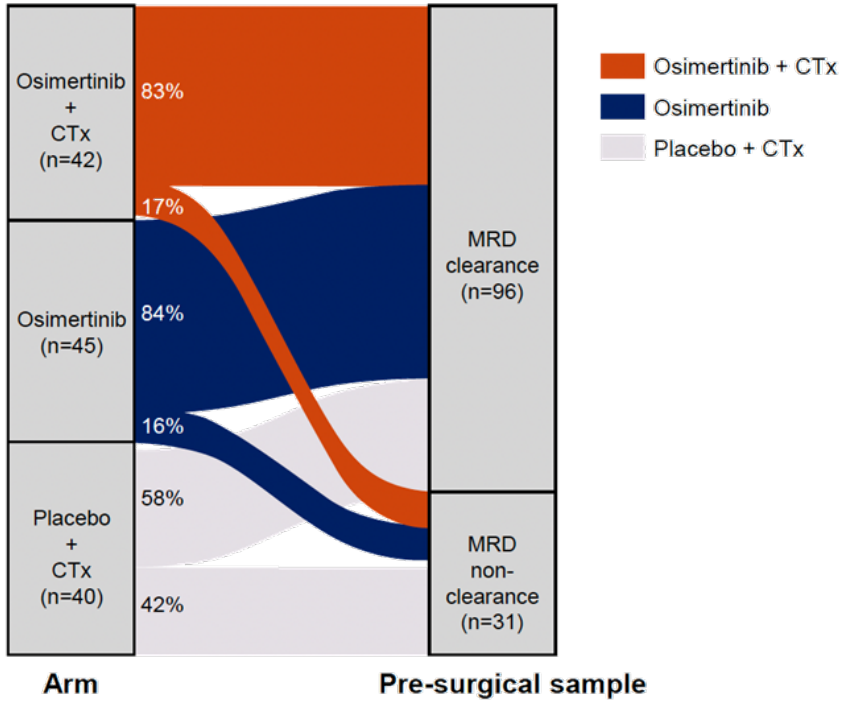
El estado basal de MTD fue un factor pronóstico para la SLE

Blakely WCLC 2025

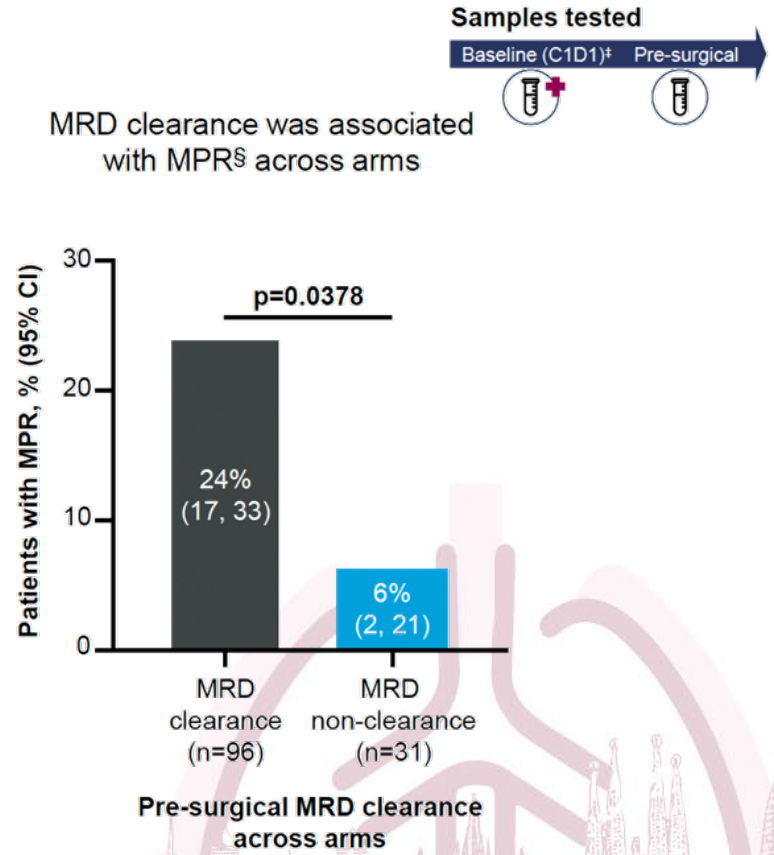
MRD en el NeoADAURA

Pre-surgical MRD *clearance* was enriched with osimertinib-containing regimens and in patients with MPR

Treatment with osimertinib-containing regimens led to higher rates of MRD clearance* vs placebo + CTx



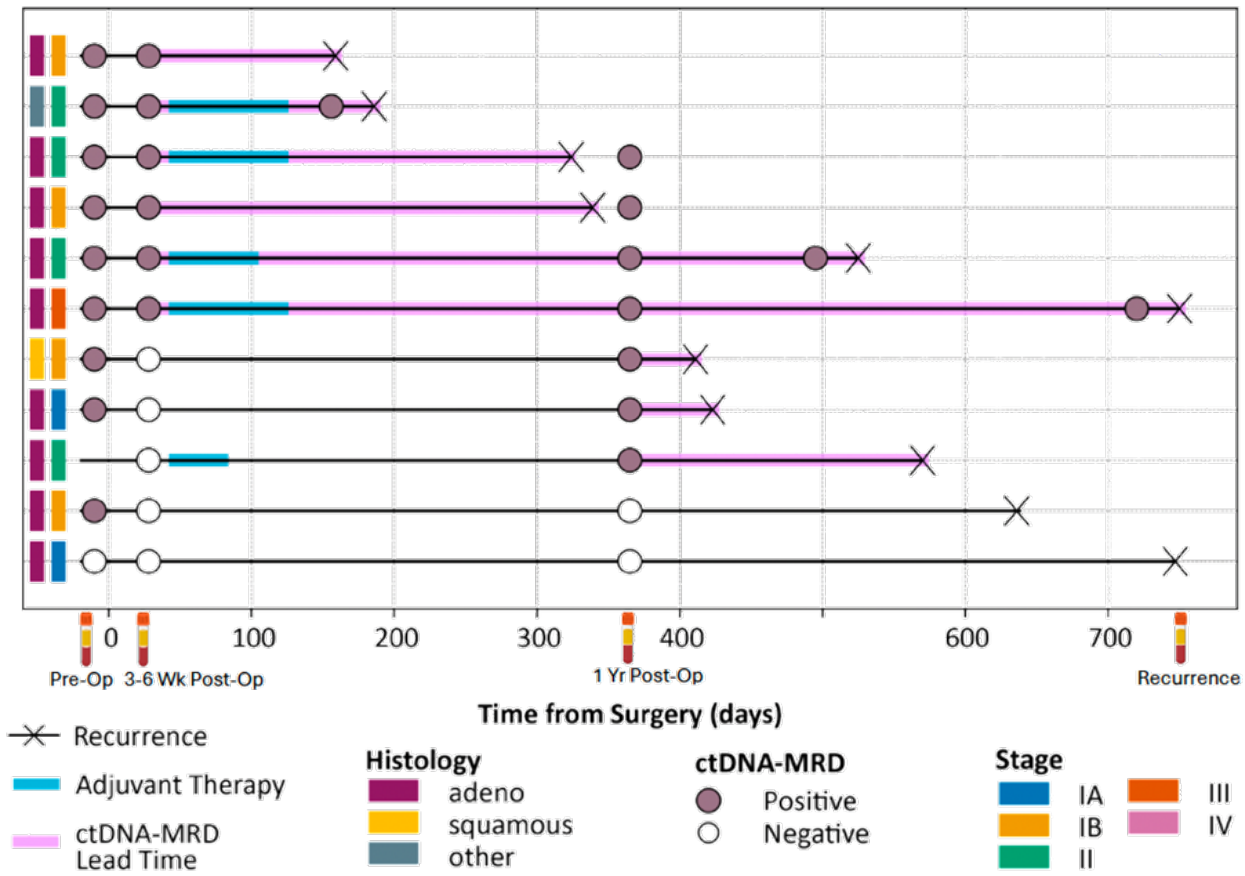
MRD clearance was associated with MPR§ across arms



MRD clearance: 10-fold decrease in ctDNA or MRD not detected in the presurgical sample after baseline MRD detected

Blakely WCLC 2025

La MRD ultrasensible mejora la detección en el CPCNP resecable en estadio I

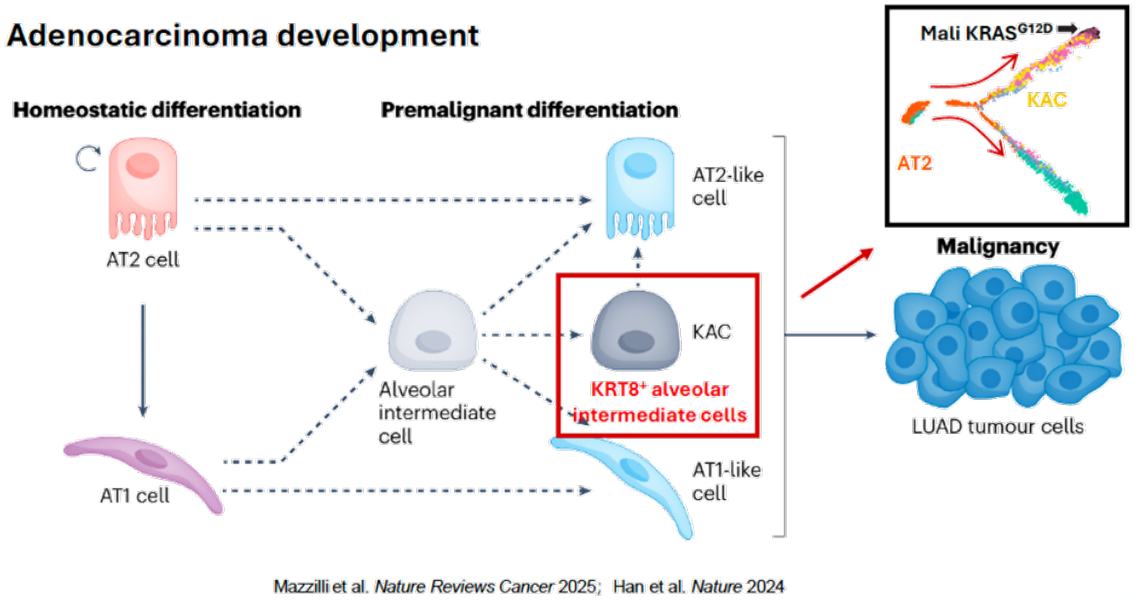


- 11 cases with recurrence assessed
- In patients with MRD detected at the post-operative landmark, the median lead-time to recurrence was 10 months
- 11/12 (92%) of samples collected within 12 months preceding relapse had MRD detected

Coyne. IASCLC 2025

Multiomic single cell profiling reveals novel evolutionary trajectories in lung carcinogenesis

Oncogenesis initiates with molecular events before the morphological changes in the tissues



Mazzilli et al. *Nature Reviews Cancer* 2025; Han et al. *Nature* 2024

Goal: To characterize tumor evolutionary trajectory, focusing on the functional plasticity in morphologically normal tissue related to MPLC development.

Can we identify the factors within the pulmonary "soil" that drive MPLC development?

Multiomic single cell profiling reveals novel evolutionary trajectories in lung carcinogenesis

Background:

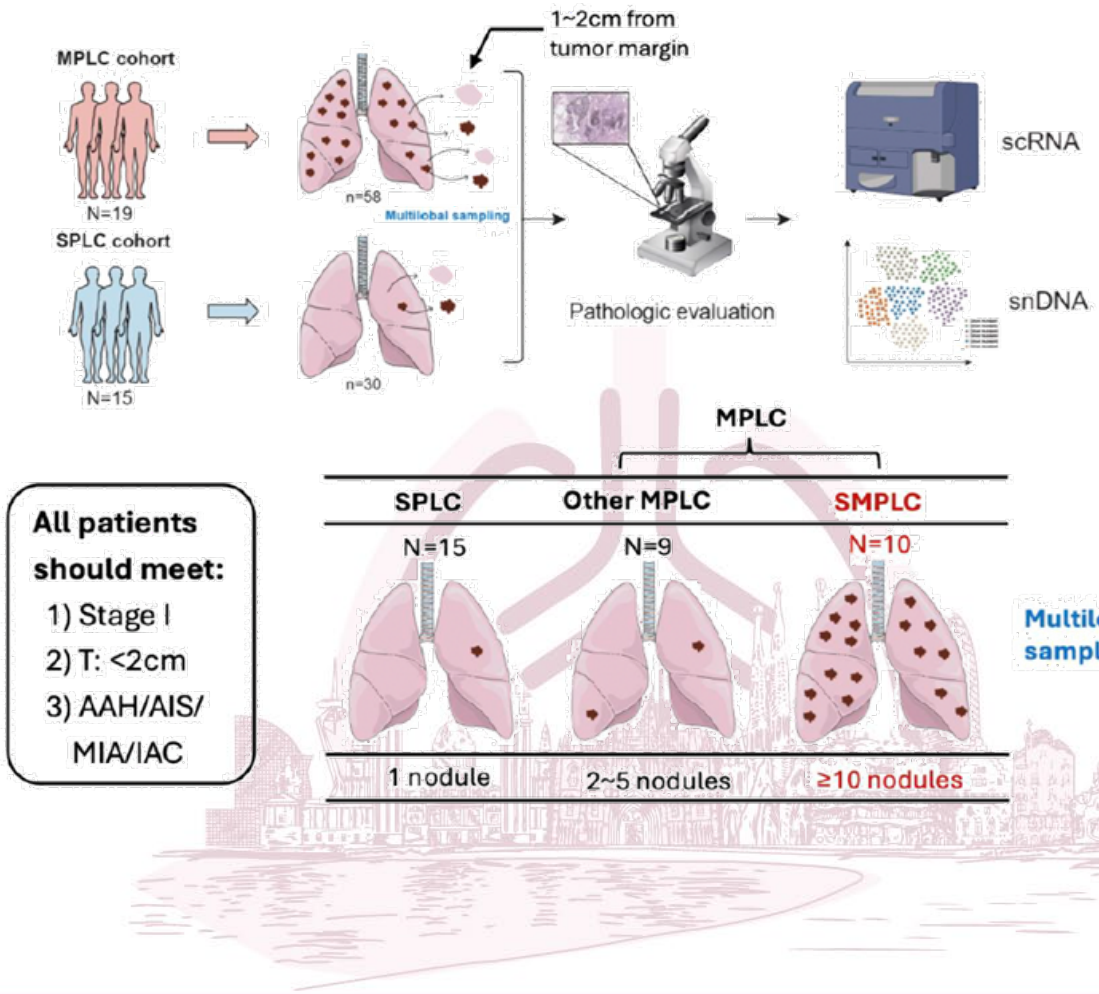
- Multifocal early-stage primary lung cancer (MPLC) is increasingly being detected.
- MPLC patients suffer from multiple pulmonary resections with substantial parenchyma loss.

Unmet clinical need

MPLC patients have limited treatment options beyond surgery.

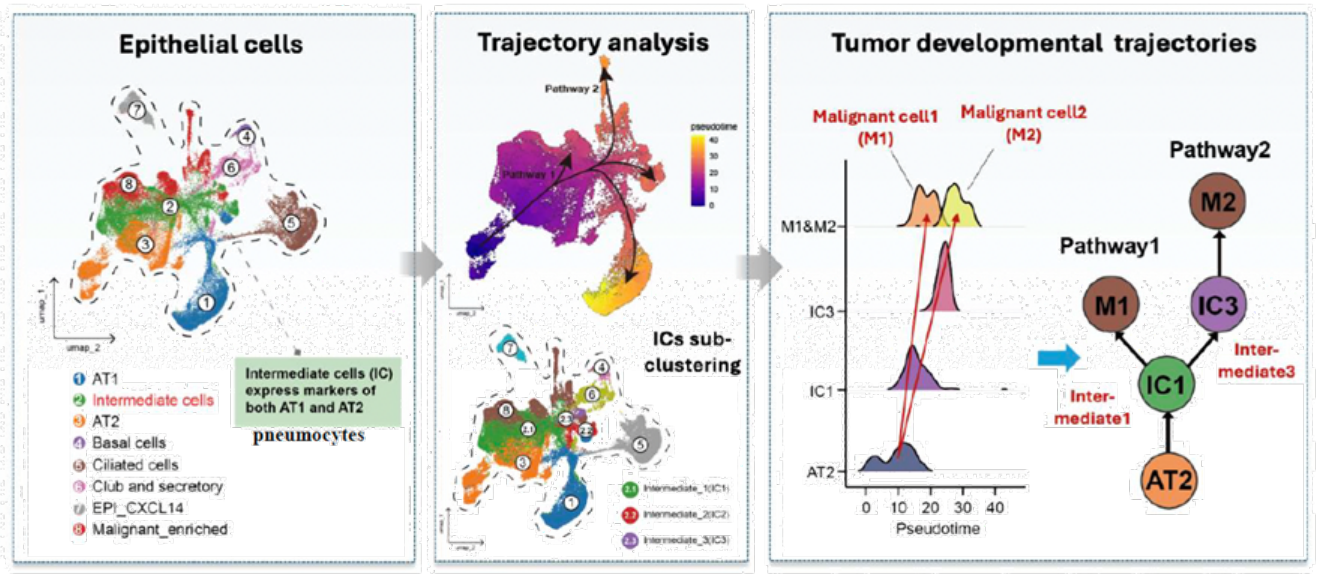
Understanding multifocal tumor developmentary trajectories is key to identifying new therapeutic targets!

Study Desing



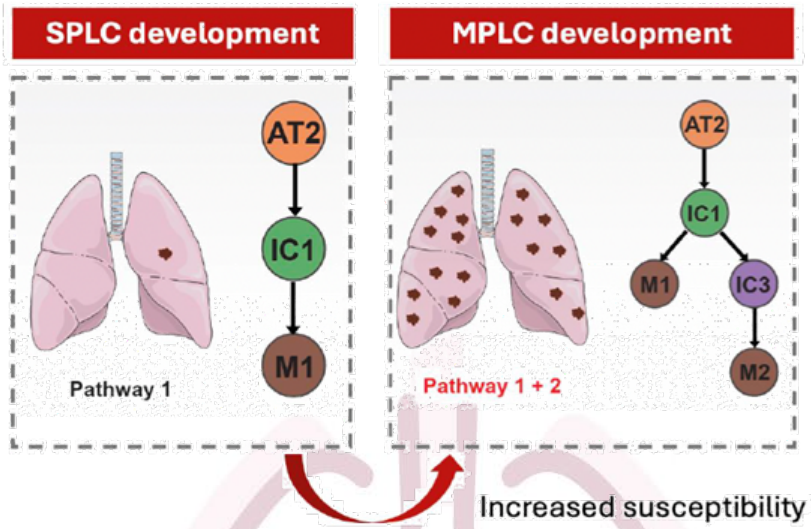
Hong. WCLC 2025

Multiomic single cell profiling reveals novel evolutionary trajectories in lung carcinogenesis



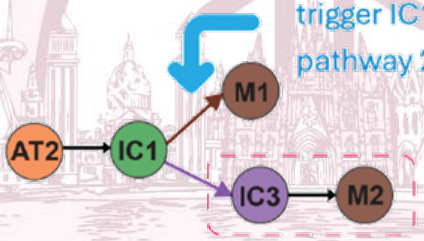
- **MPLC patients exhibit two distinct pathways that drive tumor development.**
- **Inflammation mediated by neutrophils in the pulmonary "soil" promotes MPLC development.**

Pathway 2 was specific to MPLC patients (MPLC pathway)



Increased susceptibility to tumor formation

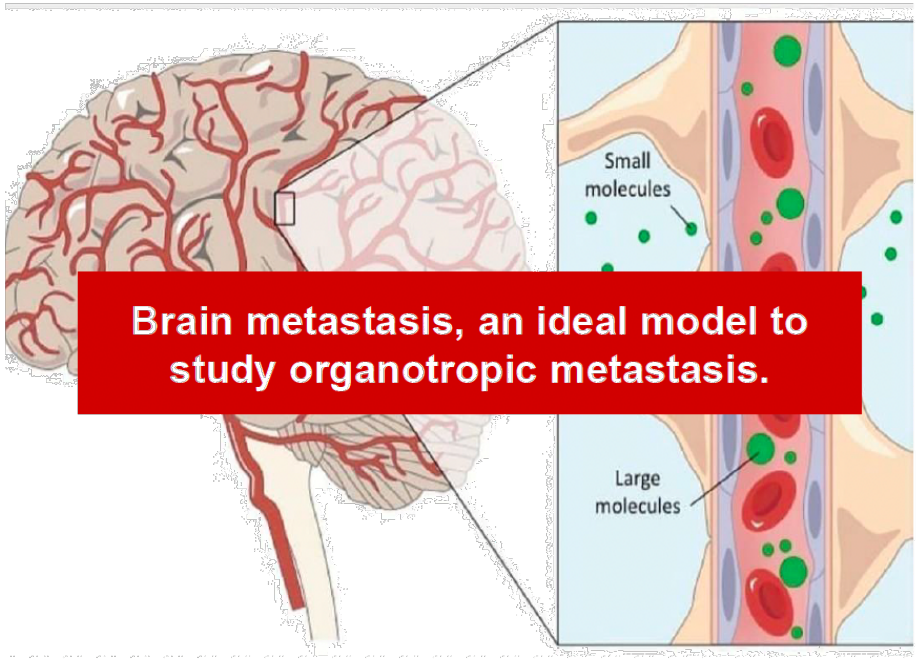
Are there any factors that trigger IC1 to generate pathway 2?



Hong. WCLC 2025

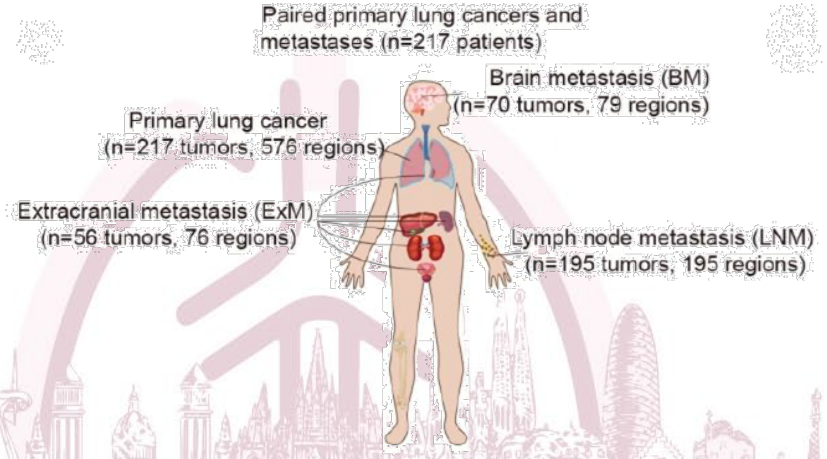
Descifrando la evolución genómica del organotropismo metastásico con cáncer de pulmón primario y metástasis

Lung cancer patients with brain metastasis exhibit worse prognosis, due to special BBB, which complicates the metastatic dynamics and also limits treatment options.



Whole-exome sequencing (WES) : large-scale paired primary lung cancers and metastases-
217 NSCLC patients with 538 tumors.

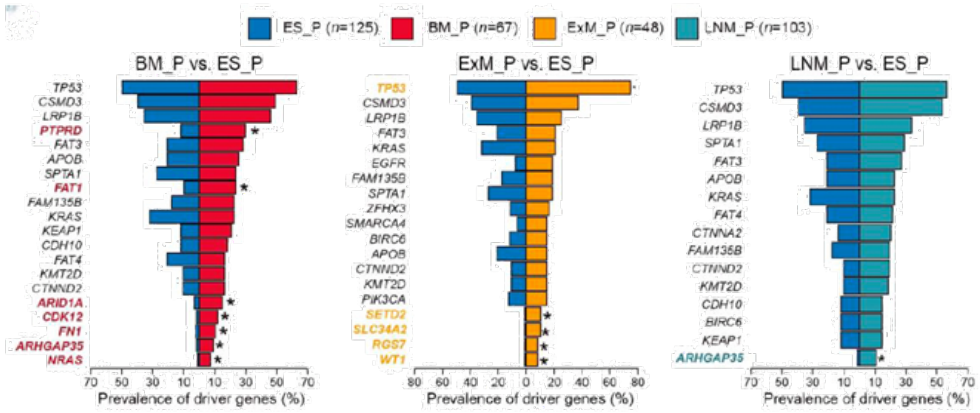
Data sources
STUDY
Jiang et al. 2021
Brastianos et al. 2015/Shih et al. 2020
Fukumura et al. 2021
TRACERx
Um et al. 2016
In-house



Xie. WCLC 2025

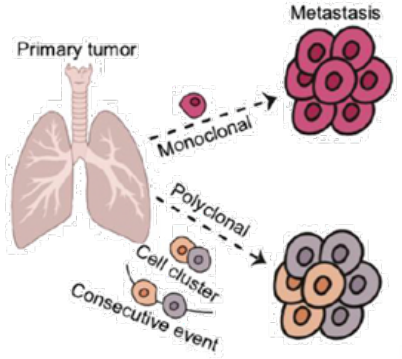
Descifrando la evolución genómica del organotropismo metastásico con cáncer de pulmón primario y metástasis

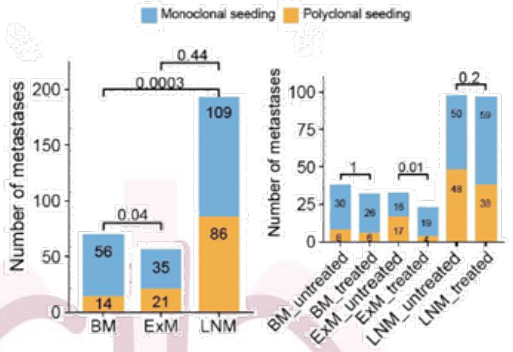
Potential driver genes: ***PTPRD, FAT1, ARID1A and CDK12*** in the brain-metastatic primary tumors. Other driver genes in ExM cohort. Furthermore, these genes were under **strong positive selection** in primary tumors



Polyclonal seeding was common in LNM (44.1%, 86 out of 195) and in ExM cohort (37.5%, 21 out of 56), **but relatively rarer in BM (20%, 14 out 70).**

Furthermore, monoclonal seeding was **more common in treated patients** than untreated patients in ExM cohort.



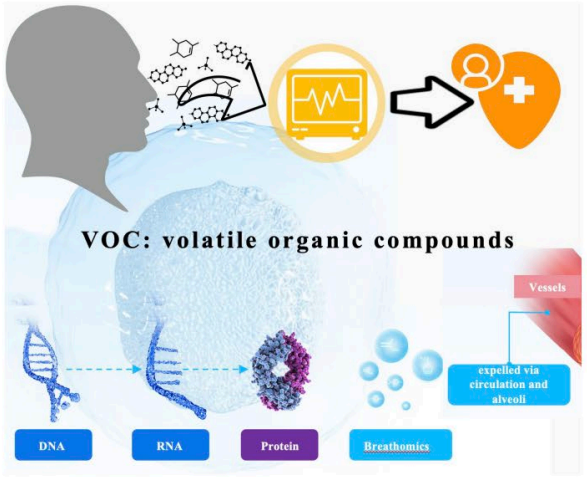


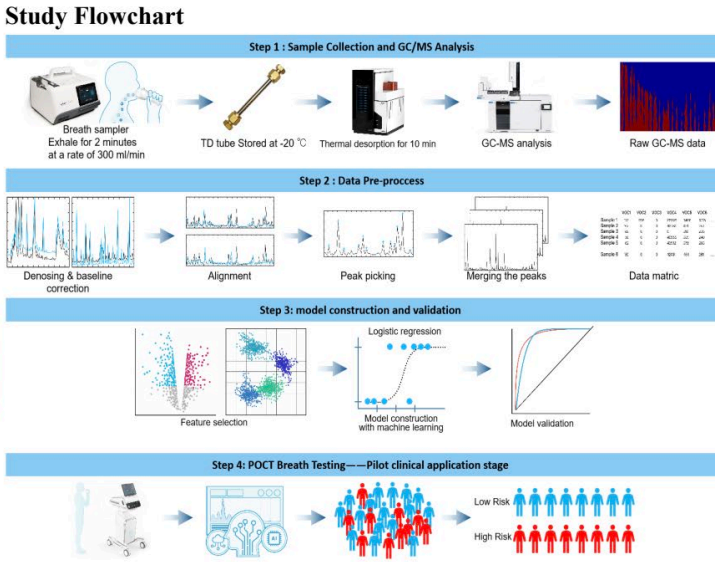
BMs experienced frequent losses of early driver mutations **through specific loss of heterozygosity (LOH)**. This suggested that **a higher level of purifying selection** was also operating during the initiation of BM.

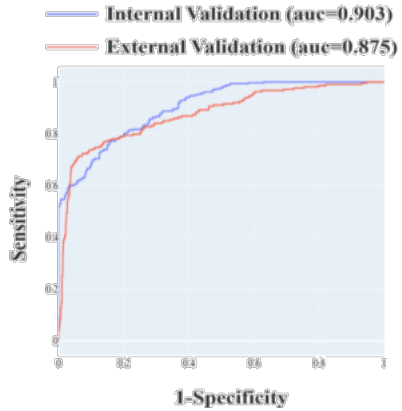
The distinct evolutionary trajectories between BM and ExM/LNM in lung cancer demonstrate that drivers of brain metastatic tropism were already **present in primary tumors** rather than being acquired during metastatic spread

Xie. WCLC 2025

Breathomics for Non-Invasive Early Detection of Lung Cancer: A Multicenter Prospective Study







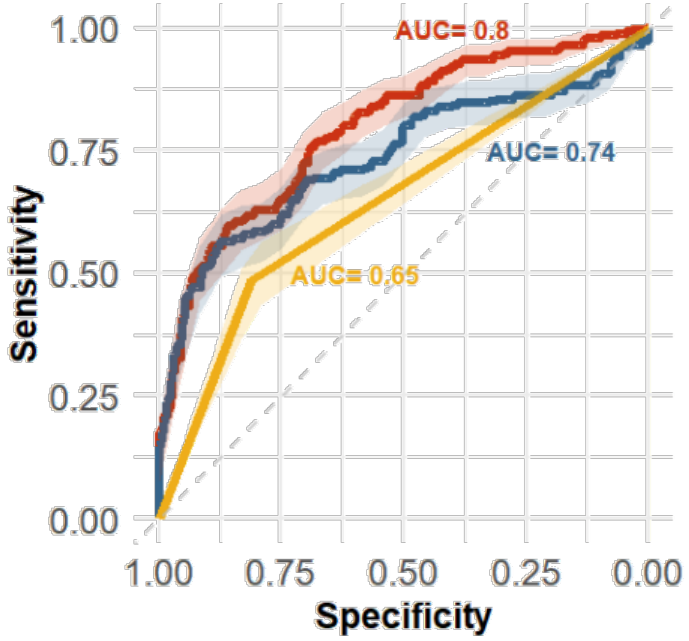
The model demonstrated high sensitivity , indicating strong capability in identifying true lung cancers.

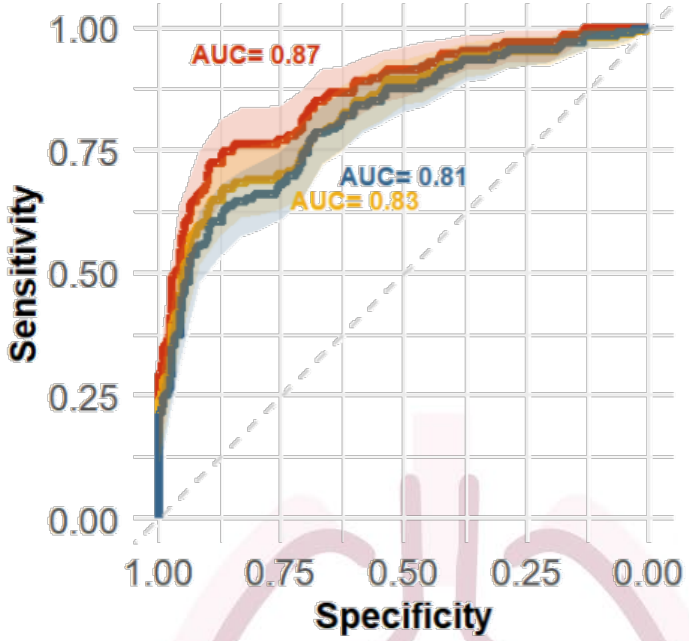
Metrics	Internal validation set	External validation set
Samples distribution	LC:381 non-LC: 373	LC: 213, non-LC： 2077
AUC	0.903 (0.881, 0.924)	0.875 (0.847, 0.904)
Accuracy	0.772 (0.771, 0.774)	0.519 (0.518, 0.520)
Sensitivity	0.947 (0.945, 0.948)	0.920 (0.918, 0.923)
Specificity	0.589 (0.585, 0.593)	0.446 (0.445, 0.447)
NPV	0.913 (0.910, 0.916)	0.969 (0.968, 0.969)
PPV	0.708 (0.706, 0.710)	0.232 (0.230, 0.234)
NPV at 2% prevalence	0.998	0.996

Wang. WCLC 2025

Integrating Circulating Protein Biomarkers in Nodule Malignancy Prediction Model

Prediction Accuracy of INTEGRAL-PEN Model





Moez. WCLC 2025

SCREENING

Comparing 74 *vs* 80 as the upper age limit for lung cancer screening: multicentre cohort study

Screen-detected lung cancer cases

- Yorkshire Lung Screening Trial (YLST) — 7,826 screened — Gabe *et al.* 2024
- Manchester Lung Health Check (MLHC) — 4,468 screened — Goodley *et al.* 2023

Primary outcome

- Overall survival from diagnosis

Comparison

- Grouped by age at last routine screen: 55-74 vs 75-80
- Treatment received

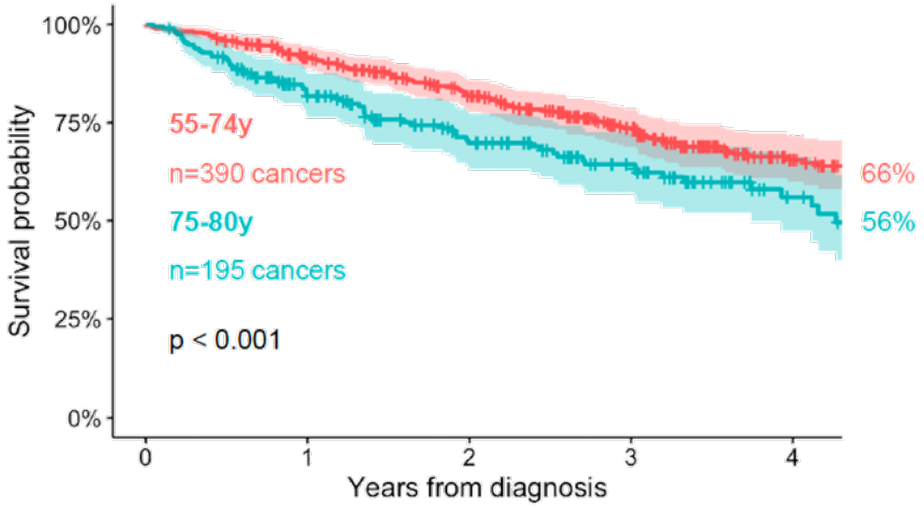
	Age 55-74	Age 75-80	
Routine screens, N	22,481	7,000	
Cancers	390	195	
Cancers per screen	1.7%	2.8%	
(95% CI)	(1.6%, 1.9%)	(2.4%, 3.2%)	χ^2 p<0.0001

Goodley. WCLC 2025

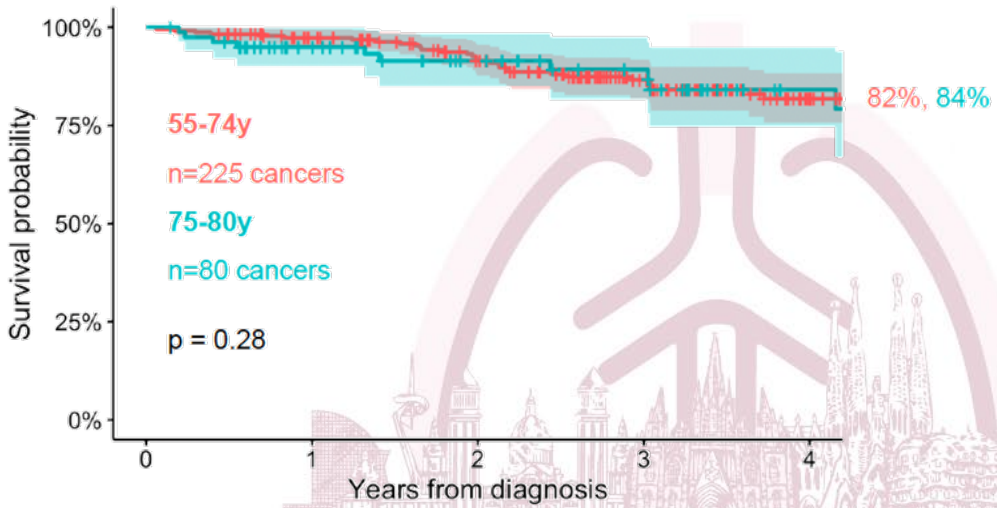
Comparing 74 *vs* 80 as the upper age limit for lung cancer screening: multicentre cohort study

Results: no OS difference after surgery

All cancers



Surgical resection



Goodley. WCLC 2025

Female Asian Nonsmoker Screening Study (FANSS): A U.S. Based Lung Cancer Screening Program in a Non-smoking Population

	FANSS	NLST	TALENT
Screened population	Asian women who never smoked	Individuals who have smoked at least 30 pack years and if former, quit in previous 15 years	Asian men and women who never smoked and additional risk factor
n	1,000	26,722	12,011
Positive Screen	Lung-RADS 3 or 4: Solid, part solid nodule ≥6mm; GGO ≥30mm	Non-calcified nodule ≥4mm	Solid nodule >6mm; GGO >5mm
Baseline LDCT Lung Cancer Detection Rate	1.3% (invasive adenocarcinoma)	1.1%	• 2.6% (includes *in situ* and minimally invasive) • 1.5% (invasive adenocarcinoma only)

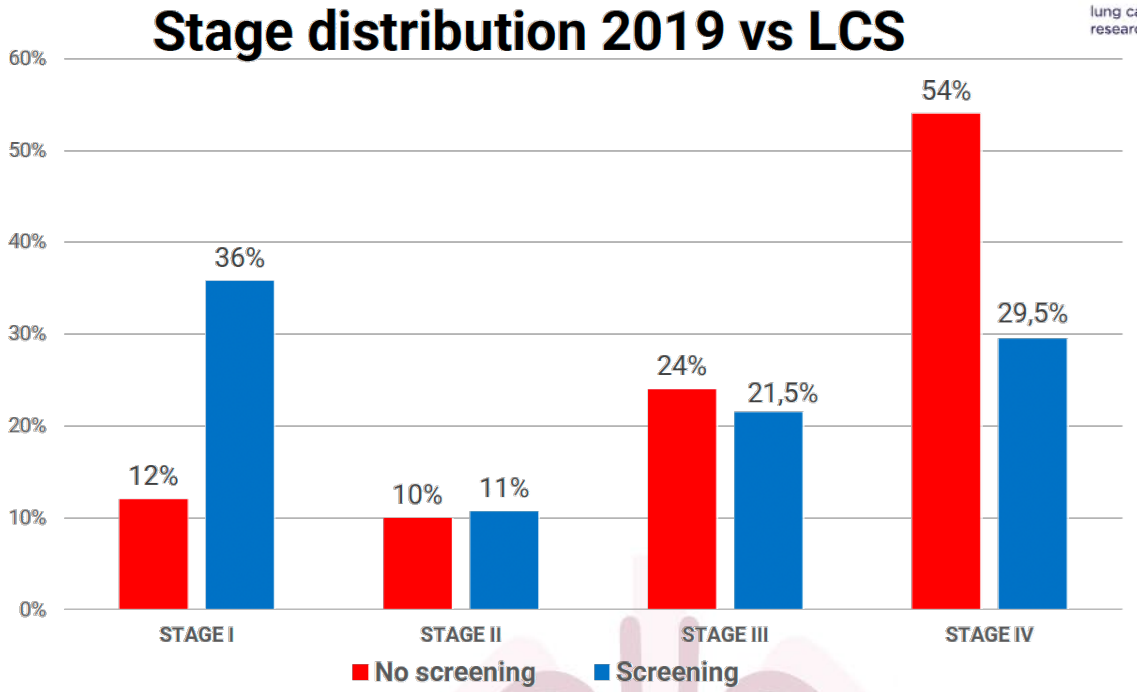
- FANSS is the largest lung cancer screening program dedicated to a non-smoking population in the U.S. and demonstrates that it is feasible.
- The FANSS lung cancer detection rate from the baseline LDCT is 1.3%, is comparable to TALENT with a selected high-risk non-smoking population (1.5%), and higher than NLST (1.1%) and NELSON (0.9%).
- All the lung cancers detected in FANSS harbor a driver mutation (EGFR or HER2).
- Development of specific screening and management guidelines for a non-smoking population compared to a population with a smoking history is necessary.
- As LCINS incidence rises, expanding lung cancer screening to those with no smoking history warrants identification of high-risk groups who may benefit.

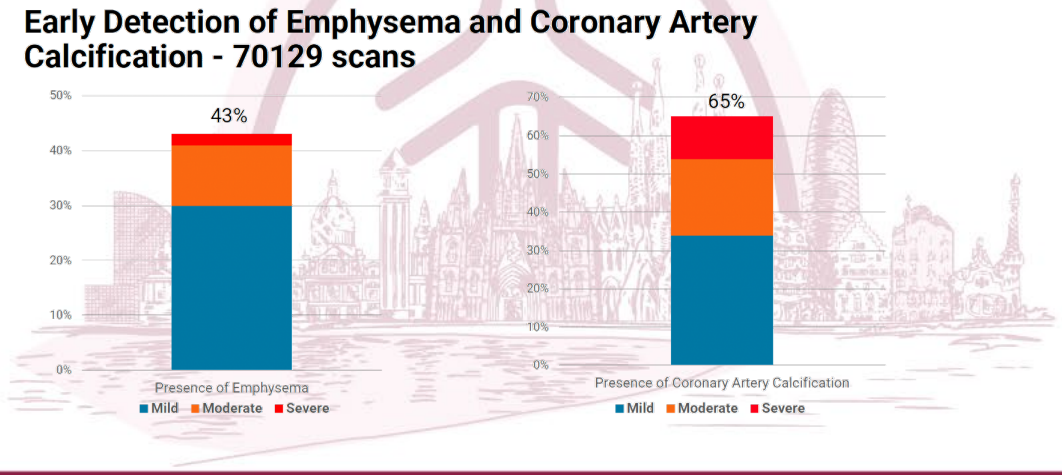
Shum. WCLC 2025

Programa Screening Croacia

Croatian LCS Program Results October 2020 – August 2025

Scans data	Semi-positive Findings	Positive Findings	Effective Radiation Dose
Total scans **70129** Baseline **50078** Follow up **20051**	6943 **9,9%** Volume 150 - 2000mm^3 Diameter 6.5 - 15.5mm	3099 **4,42%** Volume ≥2000mm^3 Diameter ≥15.5mm VDT <400 days	**0,87 mSv** (average value) **Male** 0,97 mSv **Female** 0,77 mSv **Minimum per site** 0,36 mSv **Maximum per site** 1,49 mSv
Demographics			
Male 53.6% **Female** 46.4% **Average age** 62.4			

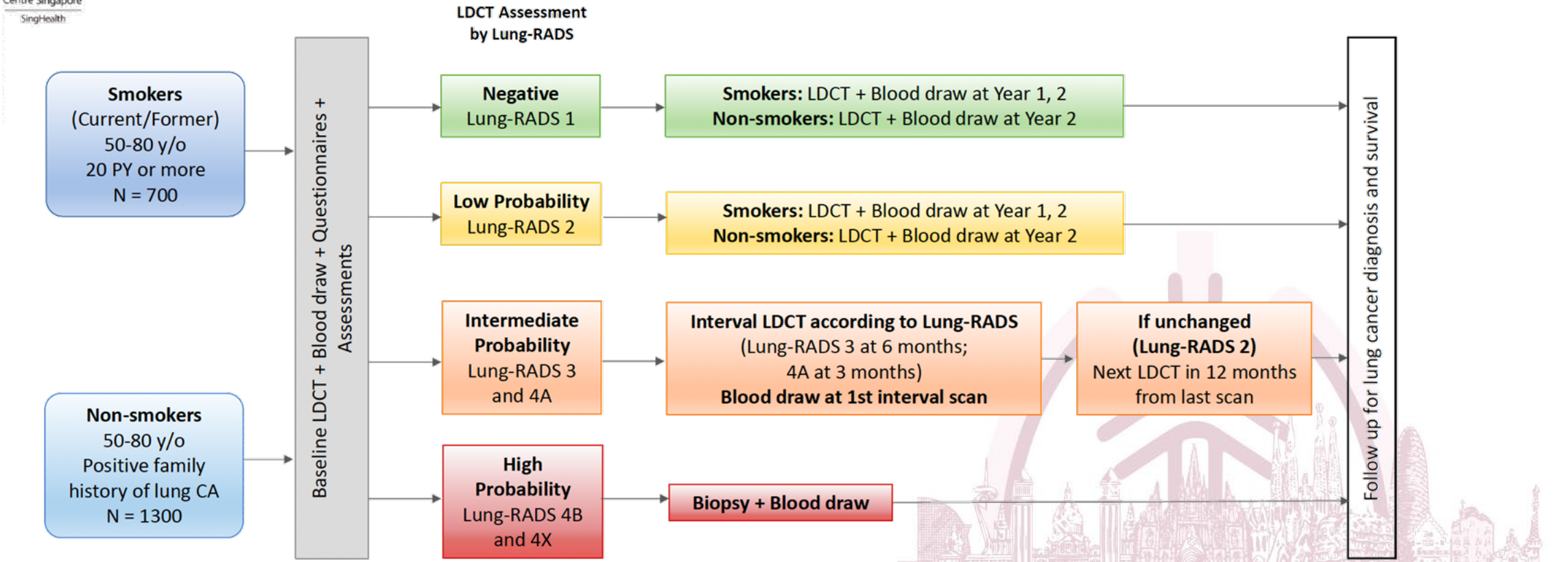




Samarzija. WCLC 2025

Programa Screening Singapur

Study Schema



Lai. WCLC 2025

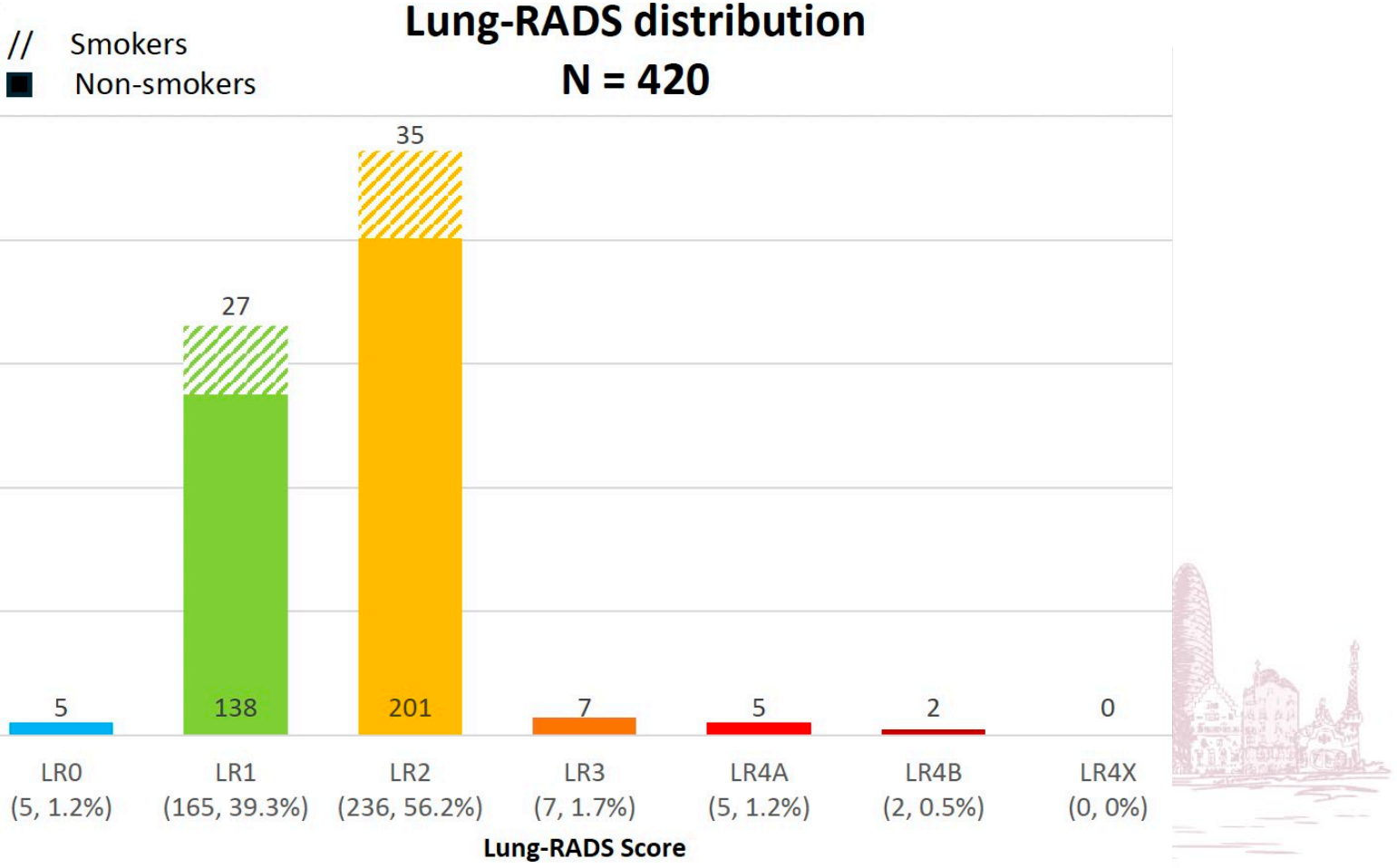
Programa Screening Singapur

Study Schema

Smokers
(Current/Former)
50-80 y/o
20 PY or more
N = 700

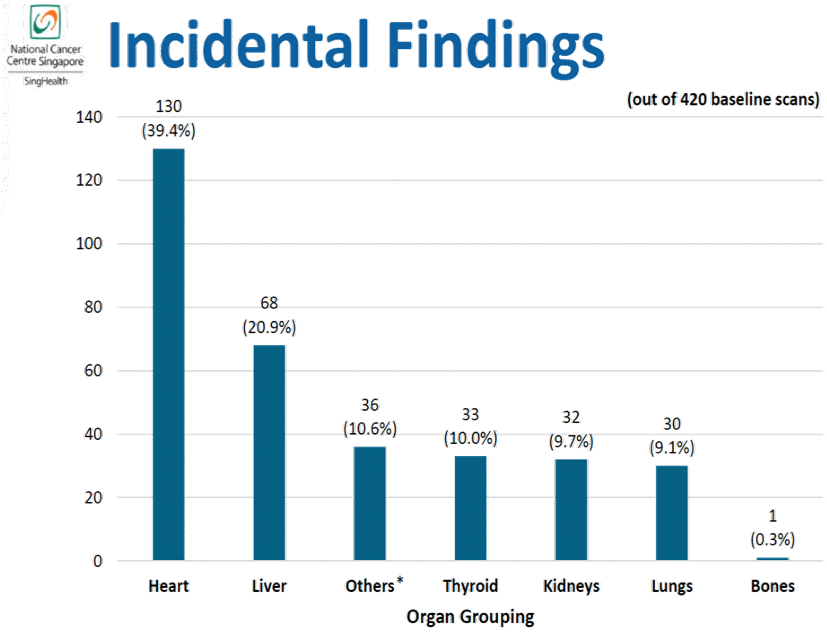
Non-smokers
50-80 y/o
Positive family history of lung CA
N = 1300

Baseline LDCT + Blood draw + Questionnaires + Assessments



Lai. WCLC 2025

Programa Screening Singapur



- **330 incidentals in 232/420 participants (55.2%)**
  - 15/330 (4.5%) potentially significant
- **Cardiac incidentals most common**
- **1 Type AB thymoma, Modified Masaoka Stage IIB**
  - Underwent surgical resection

Conclusiones

La tasa de detección del cáncer de pulmón en personas con riesgo en Singapur fue del 1,9 %.

Más alta que NLST (1,1 %) y NELSON (0,9 %) – fumadores
Comparable a TALENT (2,6 %) y FANSS (1,5 %) – no fumadores

Es necesario optimizar la estratificación del riesgo de los nódulos detectados en pantalla y las vías de gestión. Es posible que Lung-RADS no sea adecuado para regiones con predominio de GGO.

Carga sustancial de hallazgos incidentales, siendo los cardíacos los más frecuentes

Lai. WCLC 2025

FACTORES DE RIESGO

Genetic and Air Pollution Scores Identify Individuals at Elevated Risk in a Lung Cancer Screening Cohort

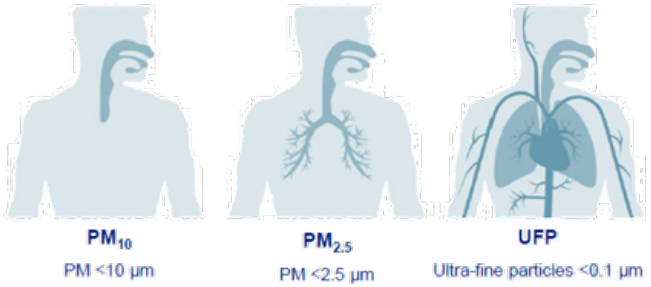
Lung cancer SNPs and ambient air pollution

Polygenic Risk Score (PRS)

- Contains lung cancer-associated SNPs
- Used in breast/prostate cancer screening, CAD
- High percentile PRS: similar risk to rare germline mutations

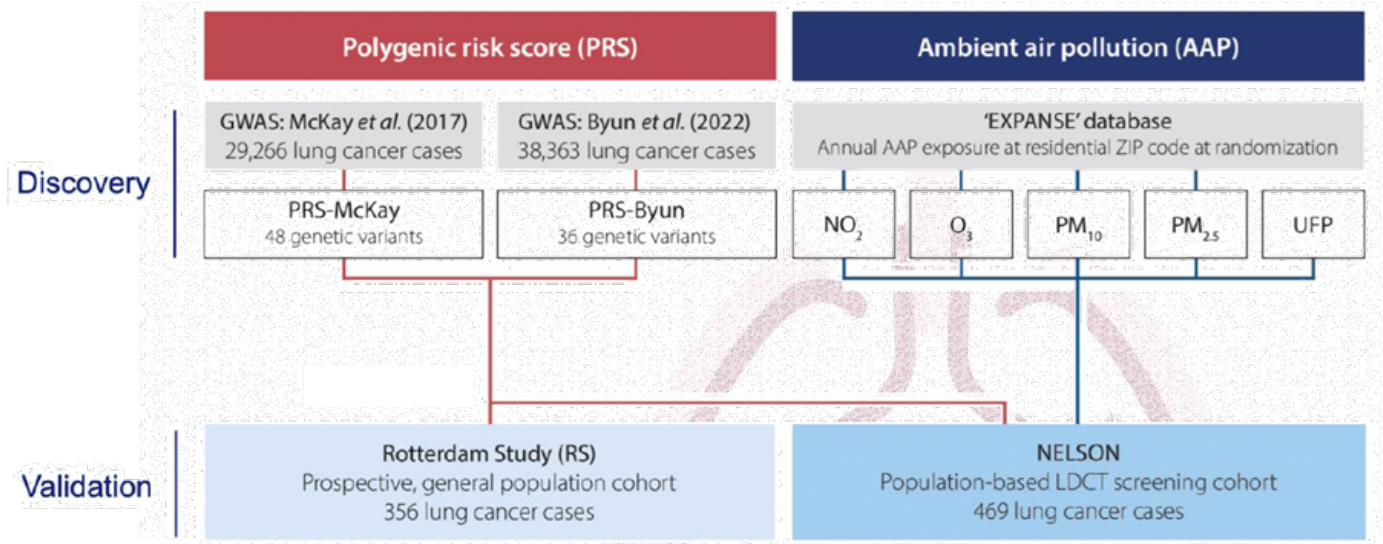
Ambient Air Pollution (AAP)

- Carcinogenic to humans (IARC Group 1)
- Strongest impact on adenocarcinoma risk
- Widely regulated pollutants: NO_2, O_3, PM_{10}, $PM_{2.5}$

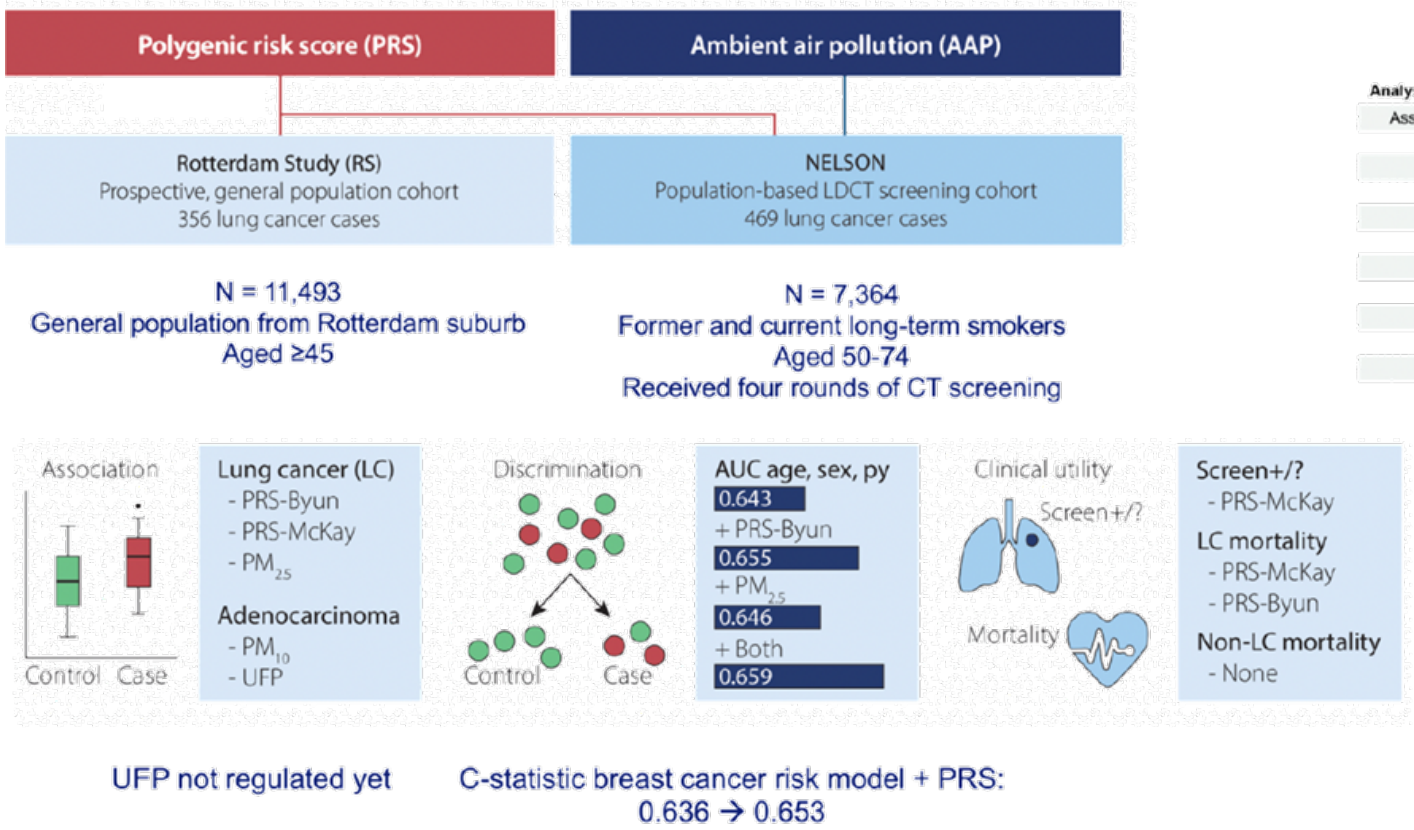


Study overview

Data collection and study cohorts



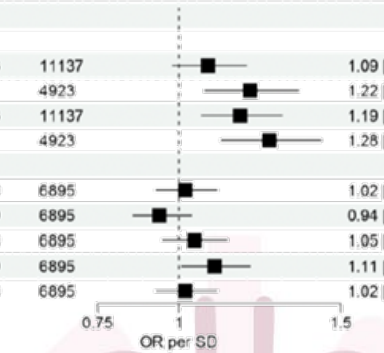
Genetic and Air Pollution Scores Identify Individuals at Elevated Risk in a Lung Cancer Screening Cohort



Predictive value of PRS and AAP

Association with and discriminative ability for **lung cancer (LC)** risk

Analysis/exposure	Cohort	Cases	Controls	OR [95% CI]	*P* value	AUC [95% CI]
Association with LC						
Polygenic risk score						
PRS-McKay	RS	356	11137	1.09 [0.98–1.21]	1.1e-01	0.523 [0.492–0.554]
	NELSON	281	4923	1.22 [1.08–1.37]	1.3e-03	0.560 [0.524–0.595]
PRS-Byun	RS	356	11137	1.19 [1.07–1.32]	1.2e-03	0.541 [0.510–0.572]
	NELSON	281	4923	1.28 [1.13–1.44]	6.1e-05	0.569 [0.533–0.605]
Ambient air pollution						
NO_2	NELSON	469	6895	1.02 [0.93–1.12]	6.8e-01	0.504 [0.477–0.531]
O_3	NELSON	469	6895	0.94 [0.86–1.04]	2.2e-01	0.512 [0.484–0.540]
PM_{10}	NELSON	469	6895	1.05 [0.95–1.15]	3.3e-01	0.514 [0.487–0.541]
$PM_{2.5}$	NELSON	469	6895	1.11 [1.01–1.22]	3.4e-02	0.529 [0.502–0.556]
UFP	NELSON	469	6895	1.02 [0.93–1.12]	6.4e-01	0.506 [0.478–0.533]



- Findings support integration PRS and AAP into lung cancer risk models
- PRS-Byun and PM identify 'true' lung cancer, not false-positives, not other prevalent causes of death

The MIRROR study: Tumor microenvironment in Patients with Non- Small Cell Lung Cancer exposed to indoor radon +/- tobacco smoke

GECP lung cancer research

Lung Cancer Risk – related to radon gas

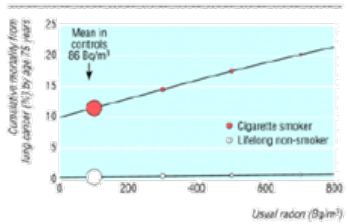
- ≈ 3-14% of lung cancer cases
- One of the leading risk factors in **non-smokers**
- **Non-threshold for safety**
- **Linear relationship:**
  ↑ exposure - ↑ time - ↑ risk
- **General population**
  ↑ 15% lung cancer risk for each 100 Bq/m³

Measure radon
Take actions if high levels
< 100 Bq/m3 in homes

World Health Organization

Lung Cancer Risk in smokers

- **Synergism** → Radon + Smoking
  ✓ 2nd cause in smokers
  ✓ ↑ x 25 risk of lung cancer in smokers



WHO Radon Book 2009; Lubin J Natl Cancer Inst 1995; Favio Bull World Health Organ 2003; Darby BMJ 2005; Krewski J Toxicol Environ Health A 2006; Lubin Int J Cancer 2004, Ruano-ravina Environ Res 2020

Observational Multicenter Prospective Cross-Sectional Study

Inclusion criteria

- **Patients with NSCLC with all stages**
  ✓ New diagnosed
  ✓ Under therapy
  ✓ Under follow-up
- **Tissue (optional)**
  ✓ Hematoxylin/Eosin s
  ✓ Tumor block*

16 different Spanish Hospitals

- **PRIMARY ENDPOINT:**
  Characterization of the **immune TME and TIL density** associated with radon exposure +/- smoking in NSCLC
- **SECONDARY ENDPOINTS:**
  Comprehensive profiling of **other immune cell pop** within the TME of NSCLC exposed to radon +/- smoking.

✓ Passive α-track detector

- ✓ Radon awareness
- ✓ Demographics
- ✓ Life-style
- ✓ Carcinogen exposure
- ✓ Clinical data
- ✓ Pathological data
- ✓ Molecular data

Tissue sample

- ✓ H/E for TME analysis
- ✓ FFPE block for Translational Research

AIM: To characterize the immune TME associated with radon +/- smoking exposure in patients with NSCLC

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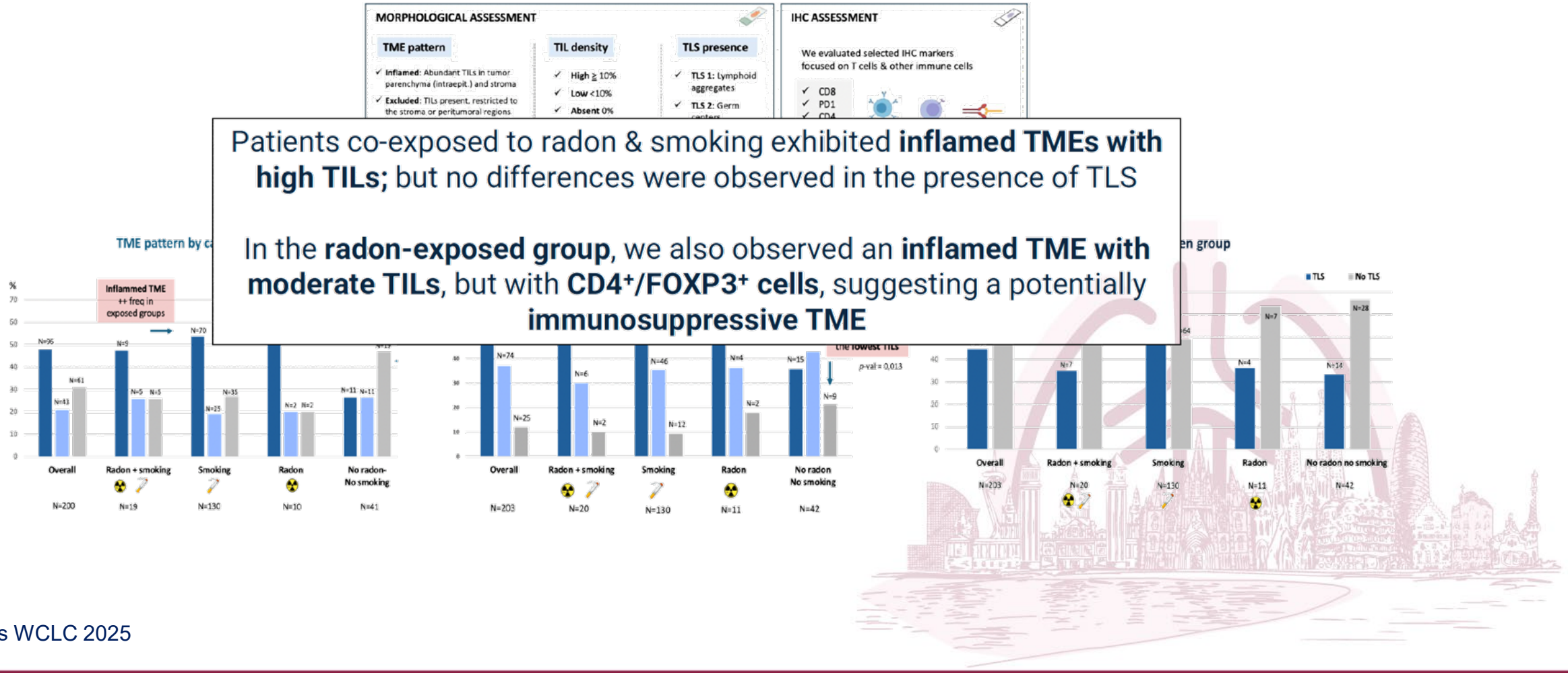
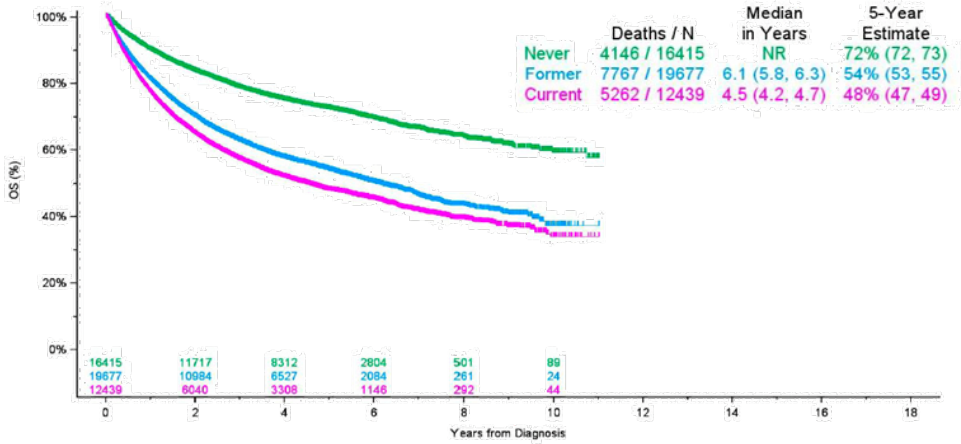


G de Herreros WCLC 2025

Impact of Smoking Status on the Prognosis of Lung Cancer in the IASLC Ninth Edition TNM Classification Database

N=48.531

Results – Influence of smoking on survival in overall cohort



Variable	Comparison	aHR (95% CI)	P Value
Smoking Status	Current vs Never	1.39 (1.34-1.46)	<.0001
	Former vs Never	1.32 (1.27-1.38)	<.0001
	Current vs Former	1.05 (1.02-1.09)	0.0052

Multivariable results are adjusted for age, gender, histology, region of world, ECOG performance score and stage.

- Similar results seen in subgroup analysis based on sex and region of the world

Variable	Comparison	Adenocarcinoma		Squamous Cell Cancer	
		aHR (95% CI)	P Value	aHR (95% CI)	P Value
Smoking Status	Current vs Never	1.45 (1.38-1.53)	<.0001	0.94 (0.85-1.05)	0.2715
	Former vs Never	1.38 (1.32-1.45)	<.0001	0.87 (0.79-0.96)	0.0078
	Current vs Former	1.05 (1.00-1.10)	0.0379	1.08 (1.01-1.16)	0.0193

Multivariable results are adjusted for age, gender, region of world, ECOG performance score and stage.

- Results not consistent in squamous cell group, likely due to greater % of later stage cases, especially among those who never used tobacco

Eng. WCLC 2025

Impact of Quitting Smoking at Diagnosis on Overall Survival in Lung Cancer Patients: A Comprehensive Meta-Analysis

25 estudios; 17800 p

Table 1. The pooled HRs for quitters *vs.* continued smokers at diagnosis, stratified by cancer stage

	Stage	Unadj HR	95% CI	p value	Adj HR	95% CI	p value
NSCLC							
	Stage I-III, only	0.42	0.25-0.72	0.002	**0.67**	**0.54-0.83**	**0.0003**
	Stage IV, only	1.17	0.77-1.77	0.47	0.49	0.09-2.75	0.42
SCLC							
	Limited stage, only	0.53	0.37-0.77	0.0008	**0.61**	**0.51-0.72**	**<0.00001**
	Extensive stage, only	0.89	0.74-1.06	0.19	-	-	-
All studies							
	Stage I-III or limited stage	0.50	0.37-0.67	<0.0001	**0.64**	**0.56-0.74**	**<0.00001**
	Stage IV or extensive stage	0.95	0.75-1.21	0.68	0.49	0.09-2.75	0.42

Lee WCLC 2025

Exposición a radón y alteraciones moleculares

GECP

N=207

Los pacientes con alteraciones moleculares tratables (excluyendo las mutaciones BRAF V600E y KRAS G12C) presentaban niveles más elevados de radón residencial (139 Bq/m3 frente a 68 Bq/m3; p < 0,001).

Aquellos con fusiones génicas tratables con fármacos tenían niveles aún más altos (144 frente a 88 Bq; p < 0,001).

- **ALK-positive NSCLC patients had higher radon exposure than ALK-negative cases (142 Bq/m3 vs. 74 Bq/m3; p=0.006).**
- **Tumors with a BRAF mutation (including non V600E) had lower exposure (39 Bq/m3 vs. 78 Bq/m3; p=0.034).**

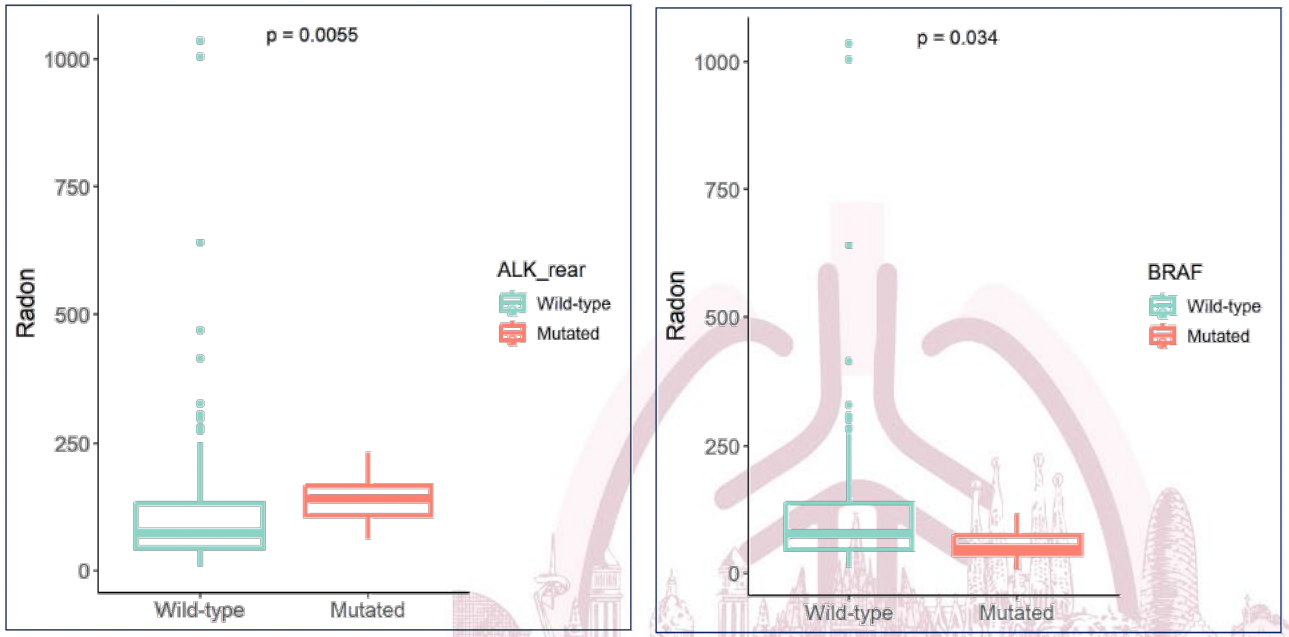


Figure 1. Association: residential radon concentration and molecular alterations

Calvo. WCLC 2025

El único viaje real de descubrimiento no consiste en buscar nuevos paisajes sino en ver con nuevos ojos

M. Proust