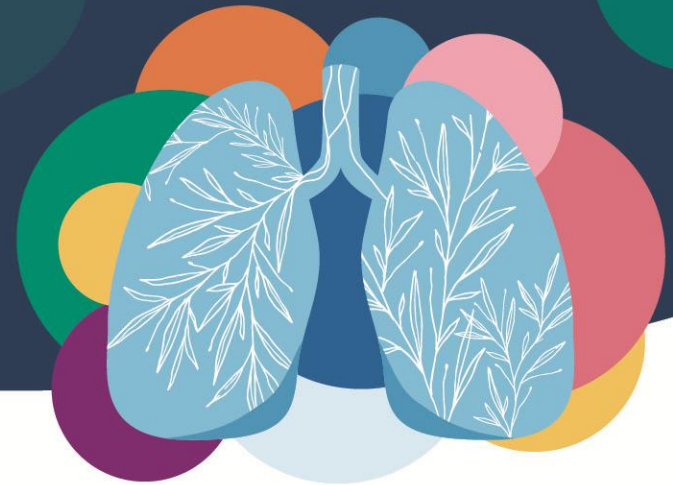
IX SIMPOSIUM ICAPEM

15 ANIVERSARIO

Asociación ICAPEM

Madrid, **28** de **octubre** de 2025

PRESENCIAL



LUNG CANCER EXPOSOME: A Roadmap to Precision Medicine

Laura Mezquita, MD, PhD

Thoracic Oncology Group, Medical Oncology Department, Hospital Clinic of Barcelona

MECA I Lab of Translational Genomics & Targeted therapies in Solid Tumors, IDIBAPS

Department of Medicine, University of Barcelona

Clínic Barcelona

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

Translational genomics and targeted therapies in solid tumors

meca Grupo de Medioambiente y Cáncer

Universitat de Barcelona

Disclosures

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Dr. Mezquita

- **Lectures and educational activities:**
  - AstraZeneca, Roche, Takeda, Janssen, Radonova, MSD, BeOne
- **Consulting, advisory role:**
  - Roche, Takeda, Janssen, MSD, Pfizer, Regeneron, Lilly
- **Research Grants:**
  - Inivata, AstraZeneca, Gilead, Foundation Medicine, Tempus
- **Travel, Accommodations, Expenses:**
  - Roche, Takeda, AstraZeneca, Janssen

OUTLINE

Clínic Barcelona | Cancer Institute and Blood Disorders

1. The Exposome in Lung Cancer
2. The ICAPEM Exposome Project
3. Challenges & future directions

OUTLINE

Clínic Barcelona | Cancer Institute and Blood Disorders

1. **The Exposome in Lung Cancer**
2. The ICAPEM Exposome Project
3. Challenges & future directions

LUNG CANCER: Multifactorial disease

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Lung cancer risk factors

- Smoking
- Indoor radon
- Air pollution
- Occupational factors
- Diesel
- Asbestos
- Metals
- Chemical substances
- Radiation
- Genetics

REALITY =
misperception

TOBACCO Stigma minimizes the others

The only risk factor

Smoking

- Indoor radon
- Air pollution
- Occupational factors
- Diesel
- Asbestos
- Metals
- Chemical substances
- Radiation
- Genetics

?

https://monographs.iarc.who.int/agents-classified-by-the-iarc/

CANCER, RESEARCH FOCUS

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Recognizing the disparity in current knowledge between genes and environmental exposures, Chris Wild (2005) defined the "exposome" representing *all environmental exposures (including those from diet, lifestyle, and endogenous sources) from conception onwards,* as a quantity of critical interest to disease etiology.

Courtesy of Dr. Kogevinas

EXPOSOME & CANCER

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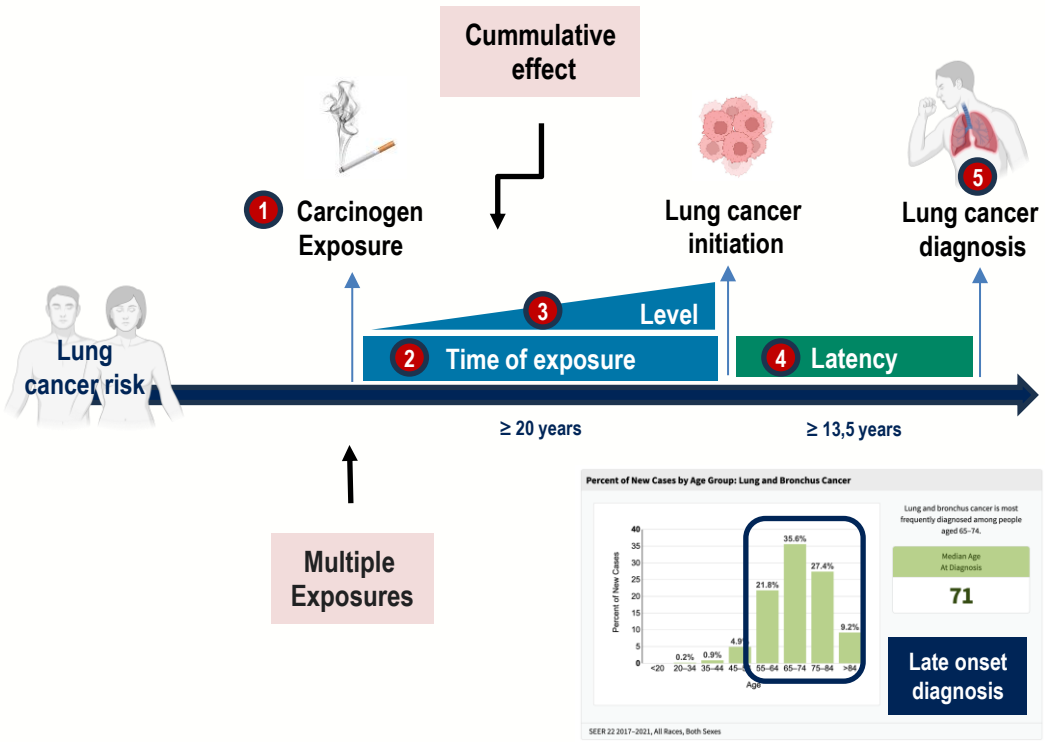
- **Environmental exposures** that an individual encounters throughout life, and how these exposures **impact biology & health**

- External factors
- Internal factors

- *Chemical, physical, biological, & social factors*

APPLICATIONS

→ **Interplay** - genetics & environment
→ **Accurate risk assessment**



Rappaport SM, et al, Envir Persp 2014, https://www.iarc.who.int/infographics/iarc-monographs-classification/;
Chen et al, Int J Environ Res Publiic Health 2023;Abecasis M et al, Leukemia (2020) 34:2279–2284; https://seer.cancer.gov/statfacts/html/lungb.html;

CARCINOGENESIS: *"one risk factor, one disease"*

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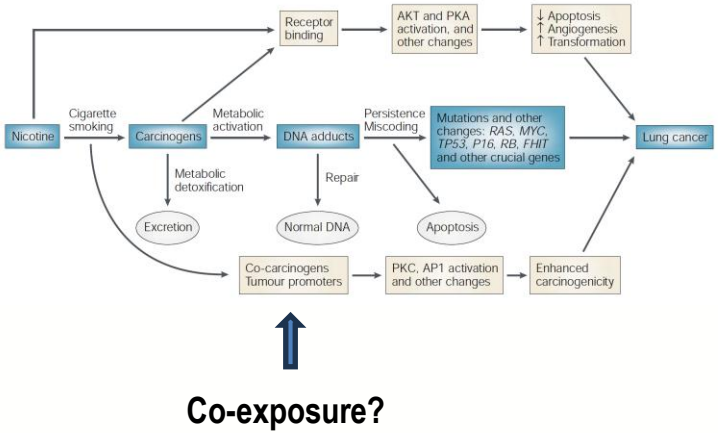
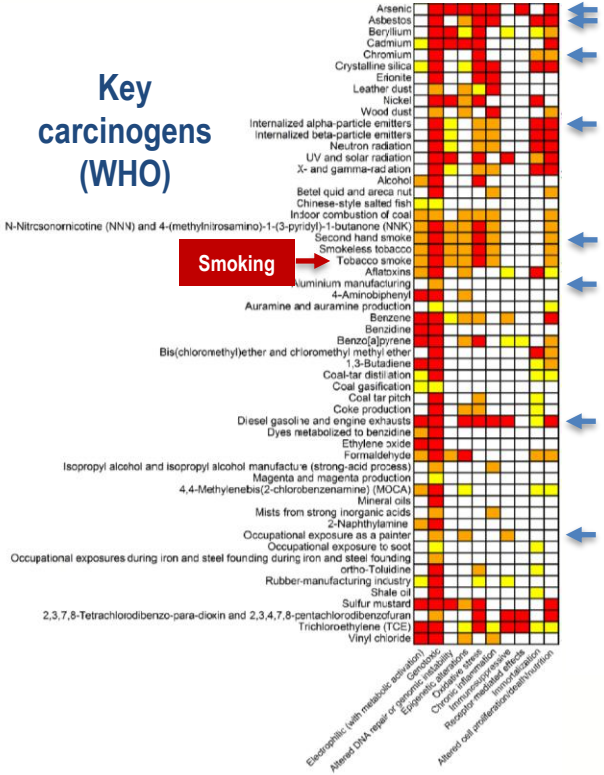
Tobacco smoking - Carcinogenesis



Co-exposure?

Key carcinogens (WHO)



Shared Mechanisms

- ✓ Metabolic activation
- ✓ Genotoxic
- ✓ Altered DNA repair
- ✓ Genomic instability
- ✓ Oxidative stress
- ✓ Chronic inflammation
- ✓ Among others

Stephen S.Hecht SS, Nature Rev 2003; Krewski D et al, IARC 2012

EXPOSOME approach

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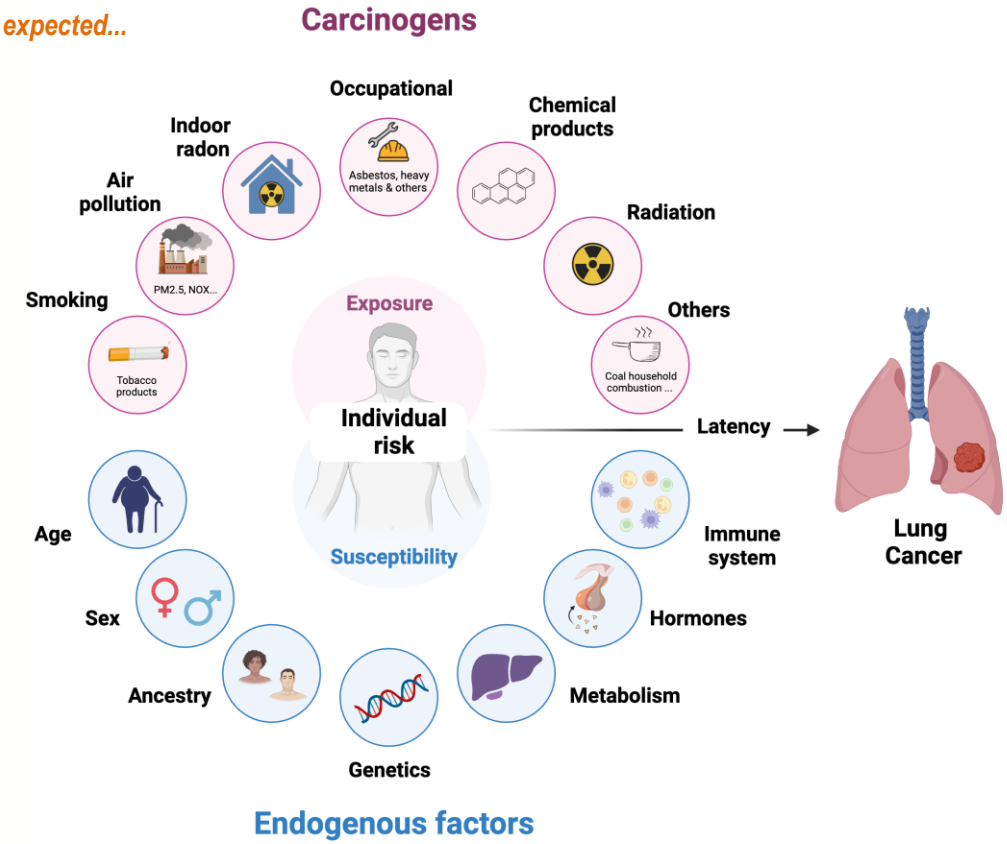
More complex than expected...



Albarrán-Artahona V et al, *manuscript in preparation*

EXPOSOME *(radon)*: Impact on cancer care?

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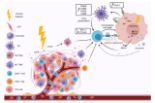
Grupo de Medioambiente y Cáncer

MIRROR

Clínic Barcelona · IDIBAPS

N= 806 patients



Dr. Garcia
Research fellow

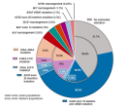
16 centers - Spain

BIORADON

EORTC — The future of cancer therapy

RadoNorm — Managing risks from radon and NORM

N= 975 patients



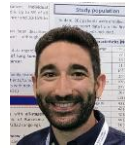
Dr. Gorria
PhD student

36 centers – 5 European Countries

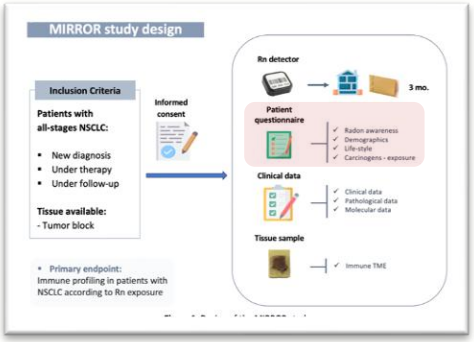
SCAN

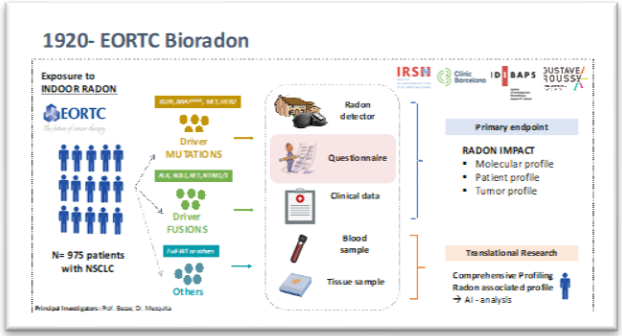
N= 380 patients

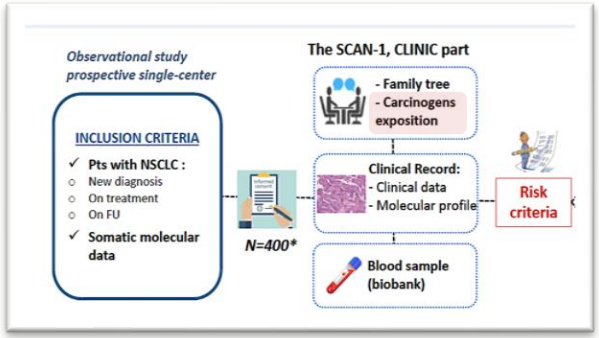
Single center - Spain



JC Laguna
PhD student







García de Herreros M, ESMO 2024, Bernabeu M, SEOM 2024, Mezquita L, ESMO 2023; Laguna JC, WCLC 2022

EXPOSOME & Impact on Cancer Care

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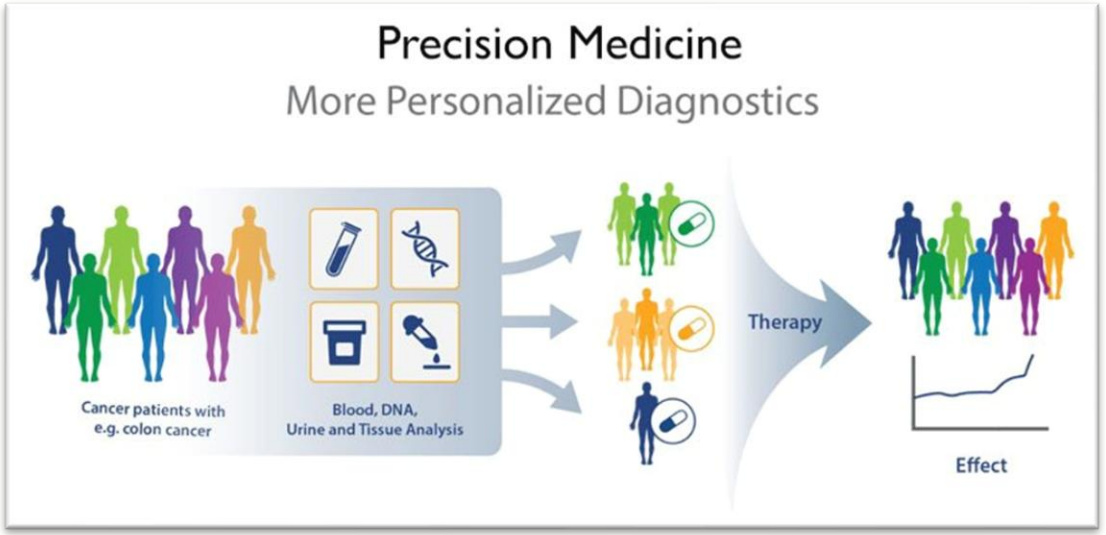
EXPOSOME:

- ↑ cancer risk
- Influence the **mechanism?**
- Influence the **profile?**
- Influence the **outcomes?**

?



More awareness
More dedicated research!

Identification of vulnerabilities

OUTLINE

Clínic Barcelona | Cancer Institute and Blood Disorders

1. The Exposome in Lung Cancer
2. **The ICAPEM Exposome Project**
3. Challenges & future directions

EXPOSOME & Precision Medicine in Lung Cancer

Clínic Barcelona | Cancer Institute and Blood Disorders

Grupo de Medioambiente y Cáncer

ICAPEM

Multicenter prospective study

INCLUSION CRITERIA

- ✓ **Patients with lung tumor regadless of histology:**
  - New diagnosed
  - Under treatment
  - Under FU
- ✓ **Good PS (PS <2)**
- ✓ **Referral by the oncologist/ICAPEM network**

PI: Dr. Isla, Dr. Mezquita

Consultation assessment

N=500

360°

- **Clinical data**
- **Carcinogens**
- **Questionnaire**
- **Blood sample**
- **Tumor sample**

Activation: Sep 2024

EXPOSOME MTB

- ✓ **EXPOSOME patterns**
- ✓ **Lung cancer profiling**
- ✓ **Genetic predisposition**

GILEAD

SOS SCLC AECC

EXPOSOME & Precision Medicine in Lung Cancer

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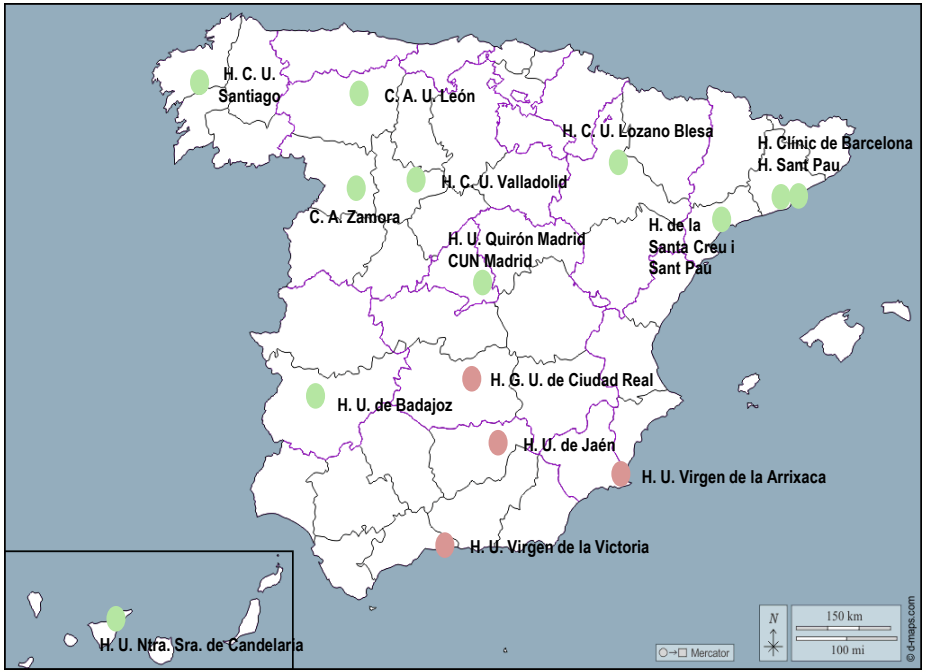
ICAPEM

16 centers participating in 9 CCAA in Spain



10 centers – *enrollment ongoing*

N	Center	PI	IRB approval	Active
1	Hospital Clínico de Barcelona	Dra. Laura Mezquita	●	●
2	Hospital Clinico Lozano Blesa de Zaragoza	Dra. Dolores Isla	●	●
3	Hospital Clínico Universitario de Valladolid	Dr. Rafael López	●	●
4	Hospital Universitario de Jaén	Dra. Ana Laura Ortega		
5	Hospital Clínico de Santiago	Dr. Luis León	●	●
6	Complejo Asistencial de Zamora	Dra. Asunción Díaz	●	●
7	Hospital Universitari Sant Joan de Reus	Dr. Sergio Peralta	●	●
8	Hospital Universitario Nuestra Señora de Candelaria	Dra. Ana Cardeña		
9	CUN-Madrid	Dra. María Rodríguez		
10	Hospital de la Santa Creu i Sant Pau	Dra. Margarita Majem	●	●
11	Hospital Universitario de Badajoz	Dra. Verónica Serrano	●	●
12	Hospital Universitario Quirónsalud Madrid	Dra Belén Rubio	●	●
13	Hospital Universitario de León	Dra. Soledad Medina	●	●
14	Hospital General Universitario Ciudad Real	Dra. Patricia Cruz		
15	Hospital Universitario Virgen de la Victoria	Dr. José Carlos Benítez		
16	Hospital Universitario Virgen de la Arrixaca	Dr. Silverio Ros Martínez		

EXPOSOME: Update in Oct 2025

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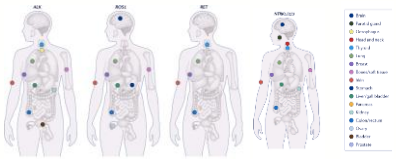
N = 216 patients

- ✓ **NSCLC**: n=180
- ✓ **SCLC**: n= 36



Data collection & Biobanking

We are here

EXPOSOME MTB

- ✓ **EXPOSOME patterns**
- ✓ **Cancer profiling**
- ✓ **Genetic predisposition**

EXPOSOME study: *One example (SCLC)*

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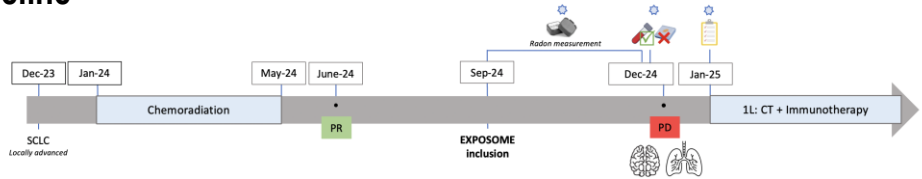
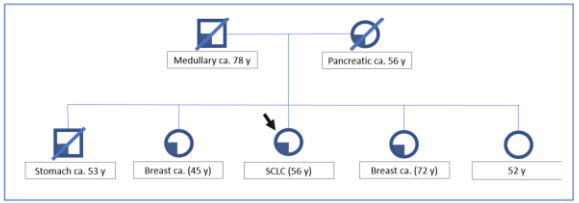
ICAPEM

Timeline

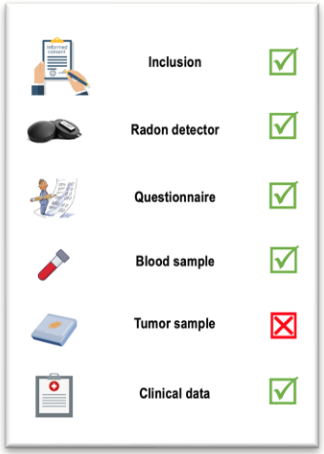
56 yo
Female
SCLC



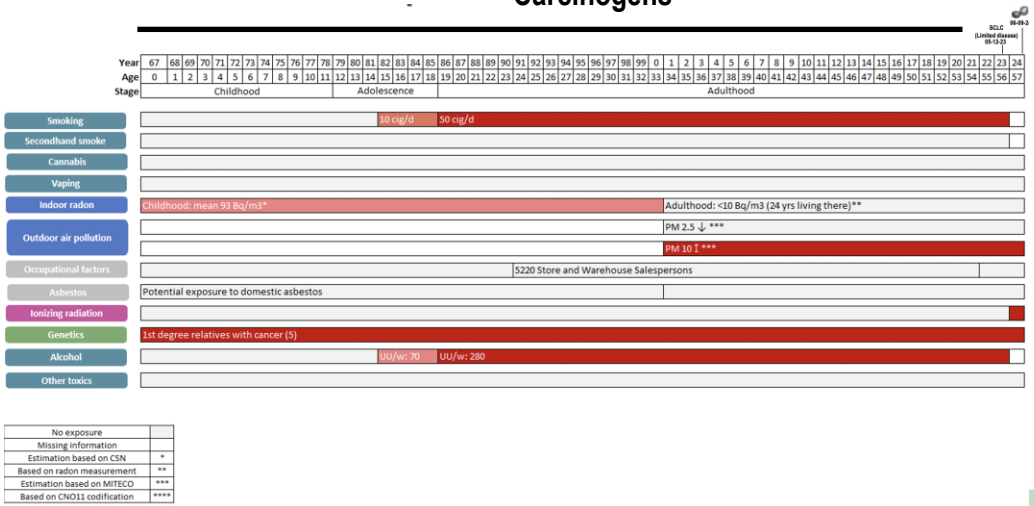
Pedigree



Procedures



Carcinogens



No exposure	
Missing information	
Estimation based on CSN	*
Based on radon measurement	**
Estimation based on MITECO	***
Based on CNO11 codification	****

Confidential; not to post

EXPOSOME study: *SCLC*

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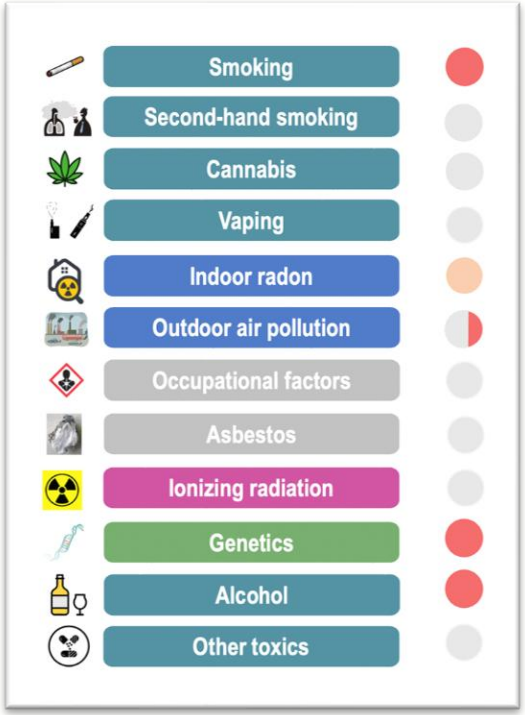
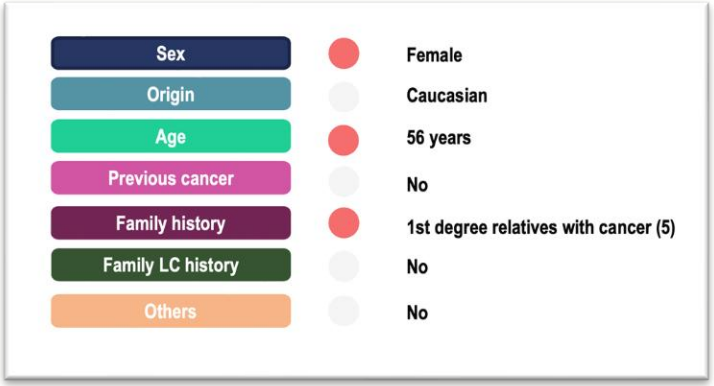
CARCINOGENS



ENDOGENOUS FACTORS



Confidential; not to post

EXPOSOME study: *SCLC*

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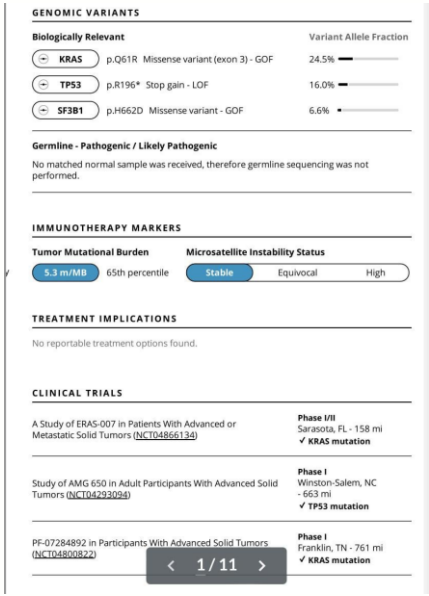
ICAPEM

REPORT

- ✓ **Variants**
- ✓ **CNV**
- ✓ **Fusions**
- ✓ Whole transcriptome
- ✓ HRD
- ✓ MSI
- ✓ TMB
- ✓ TME profiling



GENOMIC VARIANTS

Biologically Relevant		Variant Allele Fraction
KRAS	p.Q61R Missense variant (exon 3) - GOF	24.5%
TP53	p.R196* Stop gain - LOF	16.0%
SF3B1	p.H662D Missense variant - GOF	6.6%

Germline - Pathogenic / Likely Pathogenic

No matched normal sample was received, therefore germline sequencing was not performed.

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden	Microsatellite Instability Status
5.3 m/MB 65th percentile	Stable / Equivocal / High

TREATMENT IMPLICATIONS

No reportable treatment options found.

CLINICAL TRIALS

A Study of ERAS-007 in Patients With Advanced or Metastatic Solid Tumors (NCT04866134)	Phase I/II, Sarasota, FL - 158 mi, ✓ KRAS mutation
Study of AMG 650 in Adult Participants With Advanced Solid Tumors (NCT04293094)	Phase I, Winston-Salem, NC - 663 mi, ✓ TP53 mutation
PF-07284892 in Participants With Advanced Solid Tumors (NCT04800822)	Phase I, Franklin, TN - 761 mi, ✓ KRAS mutation

‹ 1/11 ›

EXPOSOME - MTB

EXPOSOME	→	Yes/No/Recommendations
GENETIC RISK	→	Yes. Germline analysis ongoing
MOLECULAR PROFILE	→	Re-biopsy (?)
IMMUNO PROFILE	→	No
TREATMENT ORIENTATION	→	No

How to identify these exposome patterns?

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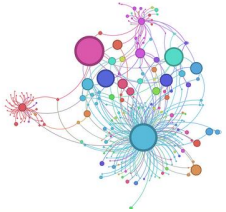


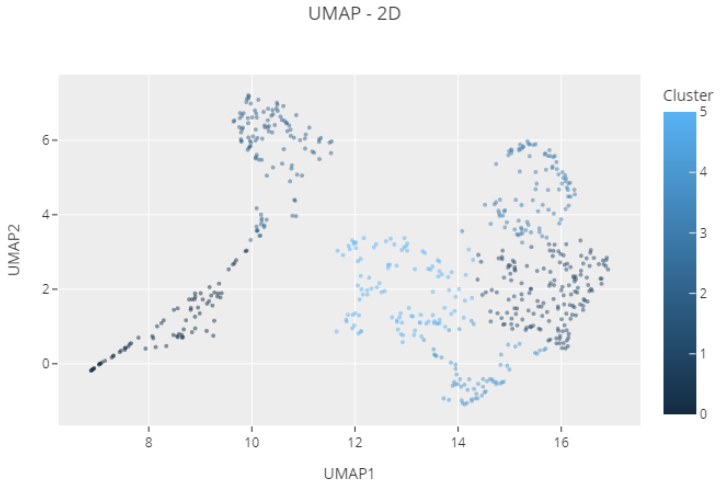
Exposome Patterns

M Ferriol
PostDoc – AI scientist

POOLED" cohort
N > 1.000 patients with
Lung cancer

EXPOSOME

- Family & personal history
- Tobacco smoking history
- Environmental exposure?
- Occupational exposure?
- Other risk factors



Model with 12 different factors – *5 Exposome clusters*

Confidential; not to post

OUTLINE

Clínic Barcelona | Cancer Institute and Blood Disorders

1. The Exposome in Lung Cancer
2. The ICAPEM Exposome Project
3. **Challenges & future directions**

Challenge n#1: In deep characterization

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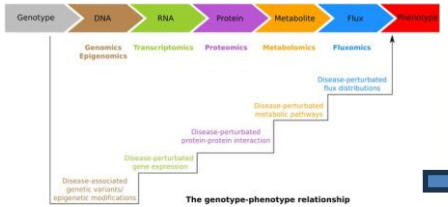
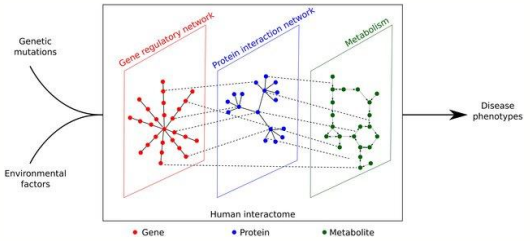
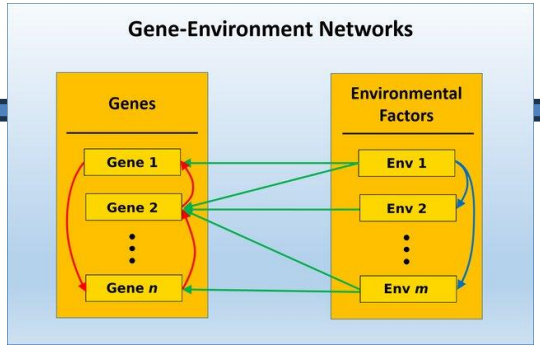
Omics
– in deep profiling

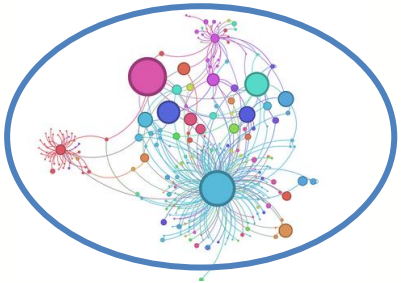




Interplay
– Exposome & endogenous factors



AI tools
- for Exposome

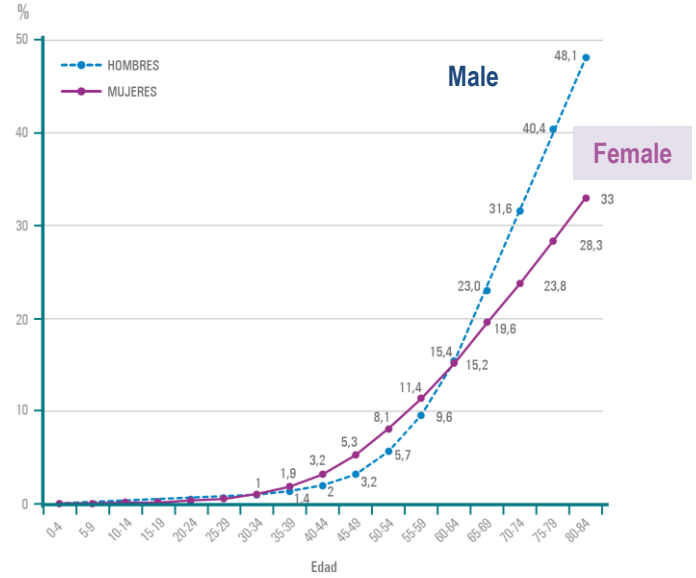


Zhang X, et al, Front Phys 2015, Kropat E, et al. Journal Dynamics Games 2020, Herrera-Luis E, et al, Nature Rev Genetics 2024

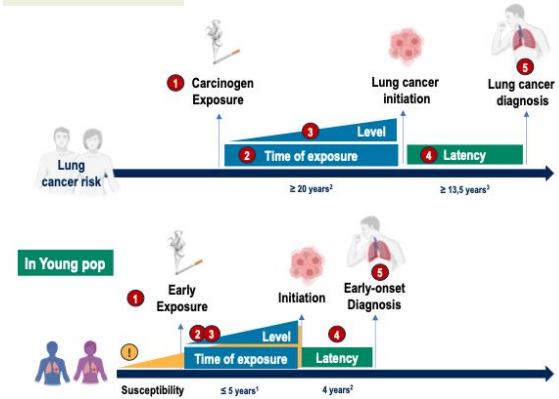
Challenge n#2: Data in understudied pop

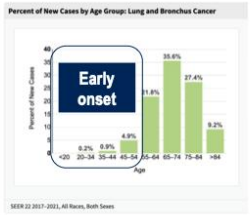
Clínic Barcelona | Cancer Institute and Blood Disorders

% of developing cancer by sex in Spain, 2025



Young pop





Susceptibility (genetics)
Early exposure (childhood)
Potent carcinogens (↓period)
Shorter latency
Lung cancer diagnosis

Cifras Cáncer 2025; Mezquita L, Educational Session ASCO 2024

Challenge n#3: Education & Communication

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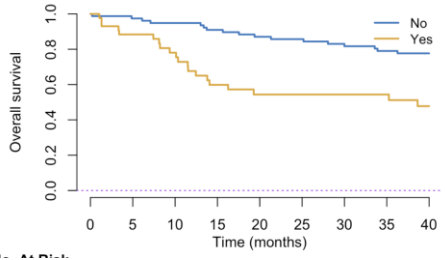
Is this relevant for <u>patients</u> with cancer?

Patients appreciate that their doctors **<u>inform them about risk factors</u>**, but with information **<u>tailored to their context</u>**

Is this relevant for <u>oncologist</u>?



Future: EXPOSOME – Preventive strategies

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Primary prevention

SHS →
Lifestyle →
Workplace →
Indoor Radon →

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

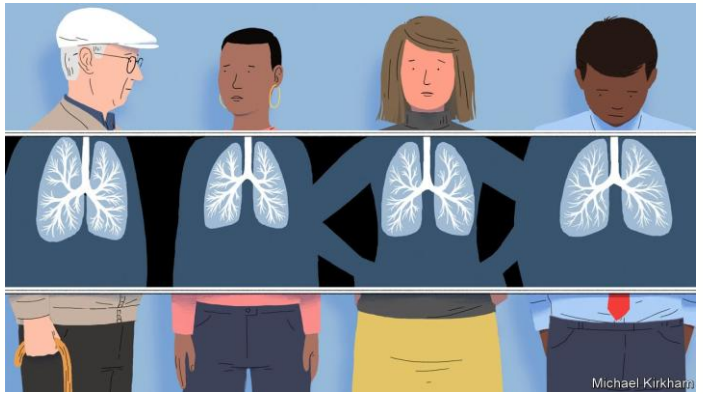
1. Do not smoke. Do not use any form of tobacco.
2. Make your home smoke free. Support smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time you spend sitting.
5. Have a healthy diet:
   - Eat plenty of whole grains, pulses, vegetables and fruits.
   - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
   - Avoid processed meat; limit red meat and foods high in salt.
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.
9. Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.
10. For women:
    - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
    - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.
11. Ensure your children take part in vaccination programmes for:
    - Hepatitis B (for newborns)
    - Human papillomavirus (HPV) (for girls).
12. Take part in organized cancer screening programmes for:
    - Bowel cancer (men and women)
    - Breast cancer (women)
    - Cervical cancer (women).

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

Find out more about the European Code Against Cancer at: http://cancer-code-europe.iarc.fr

World Health Organization

Cancer Screening



The Economist

Redefining eligibility criteria?

de Koning H, et al NEJM 202 ; Adamek M, et al. Lung cancer screening: learning from implementation, 2022;
https://cancer-code-europe.iarc.fr/index.php/es/

Future: NEXT STEPS

Clínic Barcelona | Cancer Institute and Blood Disorders

- **EXPOSOME – Molecular Tumor Board**, planned in Q1 2026
- **Full activation** soon! (IRB Approval)
- **Continuing recruitment & biobanking**
  - More centers
- **Applying to additional Grants** – for –omics analysis & biomarkers

¡GRACIAS!

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ICAPEM

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Are you interested on participate in this study?

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