

# LUCIA



Lung Cancer-related risk factors and their Impact Assessment

HORIZON-MISS-2021-CANCER-02

## LUCIA Workshop – Understanding Lung Cancer

San Sebastian, Sept. 5<sup>th</sup>, 2023



# State of the art of Lung Cancer Screening

***Juan Carlos Trujillo Reyes***

*Department of Thoracic Surgery  
Hospital de la Santa Creu I Sant Pau*



## CONFLICT OF INTEREST

### SPEAKING FEES

- Roche
- AstraZeneca
- Medtronic
- Johnson & Johnson

### SCIENTIFIC CONSULTING

- Roche
- AstraZeneca

### RESEARCH GRANTS

- **FIS**  
PI20/00154, Incidencia y relevancia clínica de la elevación perioperatoria de la Troponina I y la fracción N-terminal del péptido natriurético cerebral en pacientes sometidos a resección pulmonar
- **CANADIAN HEALTH INSTITUTE:**  
Anticoagulation for stroke prevention in patients with recent episodes of perioperative atrial fibrillation after noncardiac surgery-The ASPIRE-AF study.  
420801, Colchicine for the prevention of perioperative atrial fibrillation (COP-AF) trial  
Merck Serono
- **SEPAR:**  
REgistry and Follow up of Indeterminate Nodules using EarlyCDT (REFINE)

## ***Table of contents***

- Current evidence on lung cancer screening
- European Recommendations
- Current situation of lung cancer in Spain
- What we have done in Spain?
- CASSANDRA project
- Current status of CASSANDRA project
- The future of LC screening: risk models, biomarkers
- Conclusions



# CURRENT EVIDENCE ON LUNG CANCER SCREENING

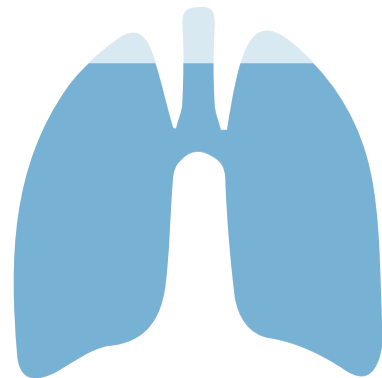
# Global incidence of lung cancer



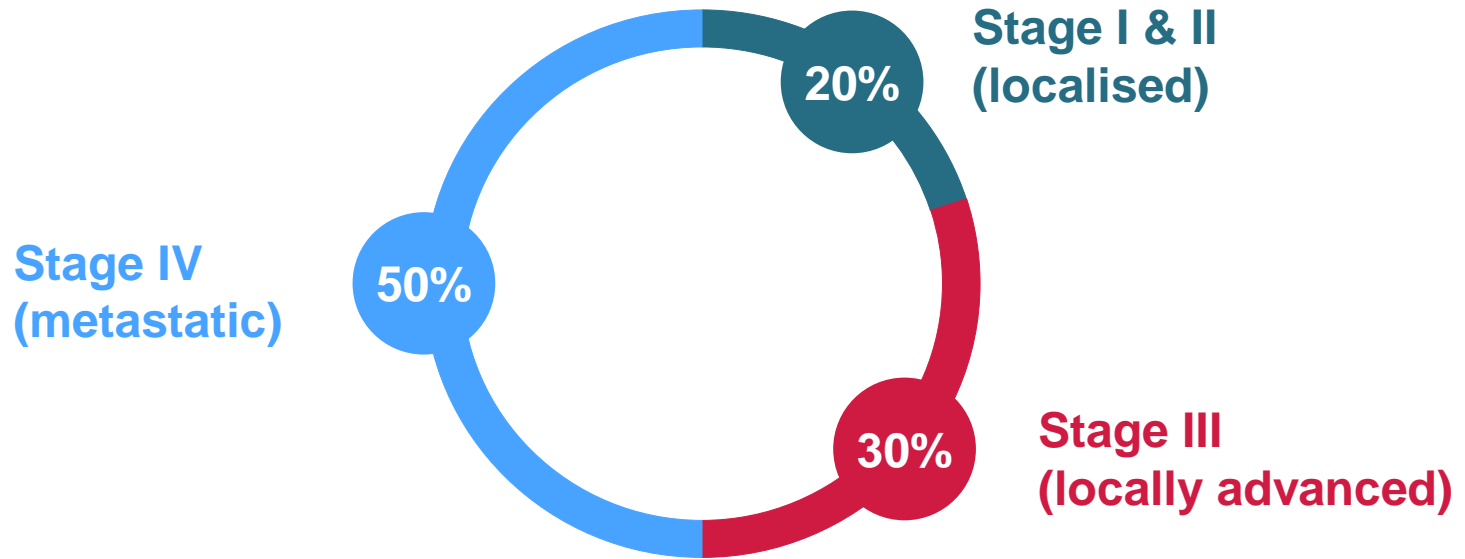
An estimated **2,206,771**  
new cases of lung cancer are  
expected **globally in 2020<sup>1</sup>**

1. *Sung, et al. CA Cancer J Clin 2021*

...of which approximately **84%**  
will be NSCLC<sup>2</sup>



2. *American Cancer Society. Cancer facts & figures 2021*



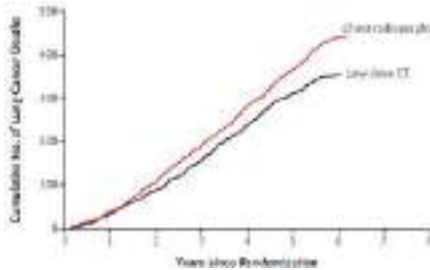


# Impact of screening on cancer mortality and overall mortality<sup>1-3</sup>



## NLST Trial<sup>1</sup>

### Lung Cancer deaths

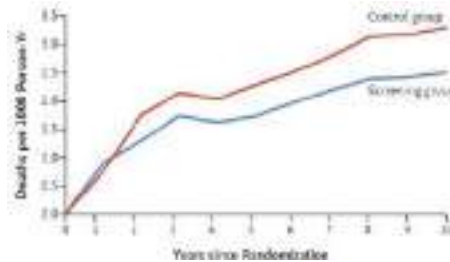


Reduction of lung cancer mortality by 20% (95% CI: 6.8 -26.7; P = 0.004) and all-cause mortality by 6.7% (95% CI: 1.2-13.6; P = 0.02) in patients screened by LDCT.



## NELSON Trial<sup>2</sup>

### Lung Cancer deaths

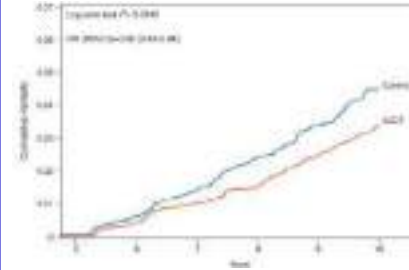


Significant reduction in LC mortality at 10-year follow-up in patients who were screened by LDCT



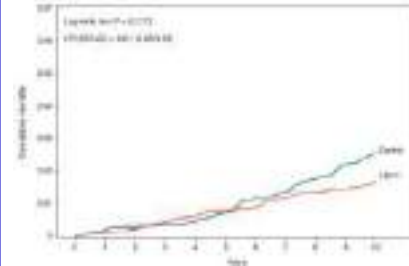
## MILD Trial<sup>3</sup>

### Overall mortality



Reduction of all-cause mortality by 20% (HR 0.80; 95% CI: 1.2-13.6; P = 0.02) (HR 0.80; 95% CI: 1.2-13.6; P = 0.02) in patients screened with LDCT

### LC deaths

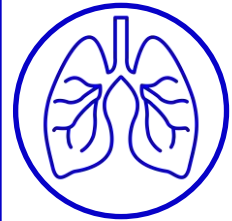
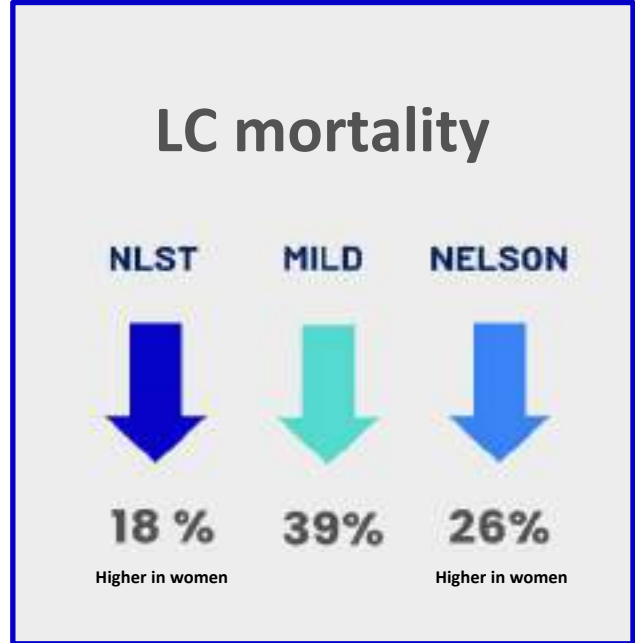
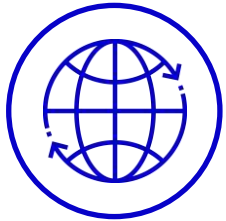


39% reduction in LC mortality (HR 0.61; 95% CI 0.39 -0.95) in patients screened with LDCT.



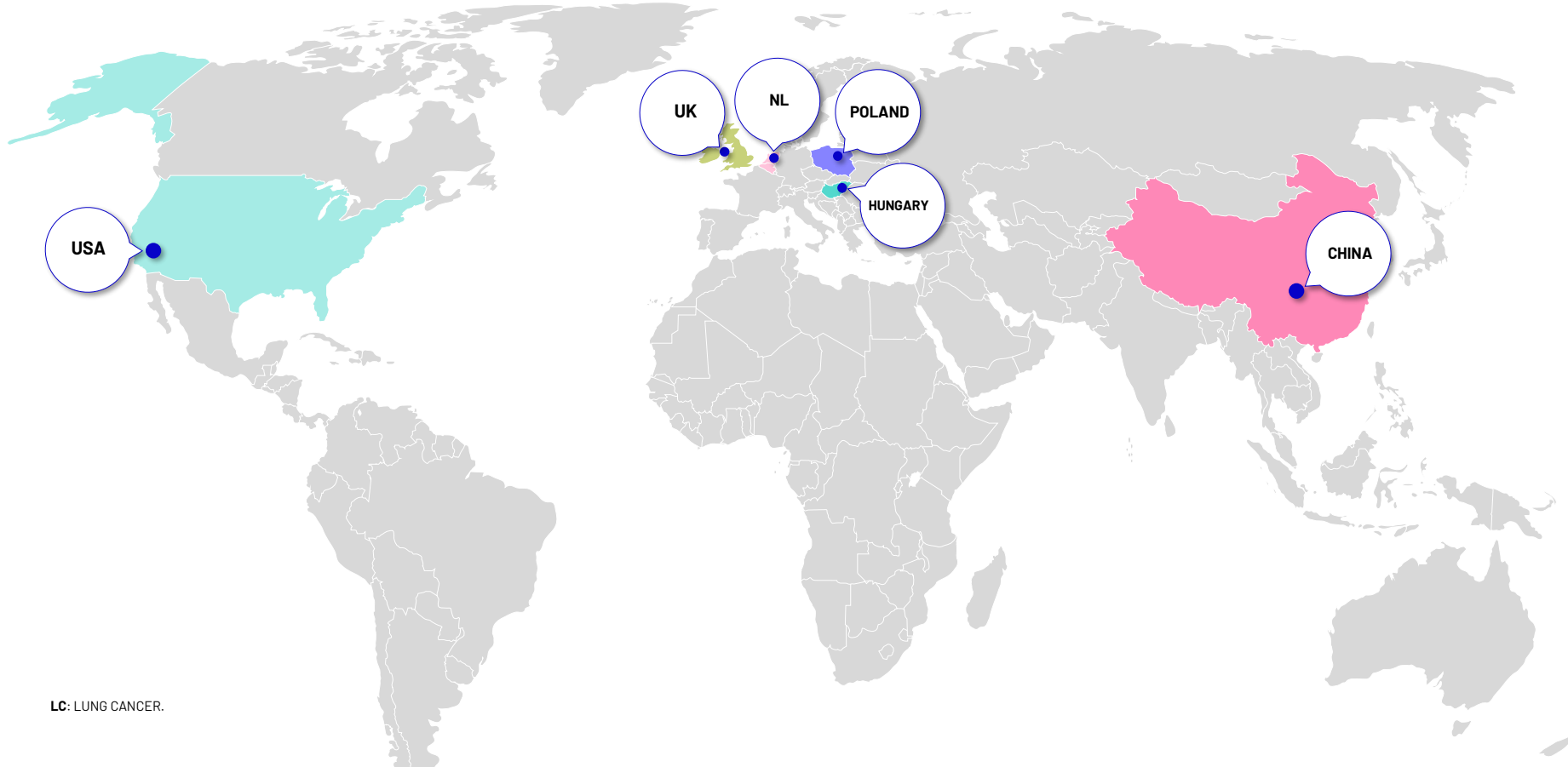


# Impact of screening on cancer mortality and overall mortality<sup>1-3</sup>





# LC screening around the world



LC: LUNG CANCER.



# EUROPEAN RECOMMENDATIONS





# Europe's position in the fight against cancer<sup>1-3</sup>



**European Parliament  
Special committee on Beating  
Cancer - 2021<sup>1</sup>**

- (...) Calls for the evidence that proves the positive effect of **targeted lung cancer screening on mortality to be recognized**
- Encourages the Council (...) to consider including lung and prostate cancer screening in the update of the Council recommendation in 2022

**LDCT:** low dose computed tomography.

1. European Parliament: Special Committee on Beating Cancer. Report on strengthening Europe in the fight against cancer – towards a comprehensive and coordinated strategy'. 2021;



# Europe's position in the fight against cancer<sup>1-3</sup>



## Science Advice for Policy by European Academies (SAPEA) - 2022<sup>2</sup>

- (...) **LDCT lung cancer screening is highly effective in reducing the burden of lung cancer mortality** when offered to **smokers or ex-smokers of both sexes in the age range 50–80**.
- The amount **of overdiagnosis, overtreatment and other harms are limited**
- Screening should include **high-risk current and ex-smokers**
- We consider that there is a strong scientific basis for **extending screening programmes to lung cancer screening by low-dose CT scanning** based on effectiveness and mortality burden









# Europe's position in the fight against cancer<sup>1-3</sup>



## WHAT ARE THE NEW EU RECOMMENDATIONS?

Extending access to targeted cancer screening for breast, colorectal and cervical cancers along with a step-by-step approach to introducing prostate, lung and gastric cancer testing.

 <p><b>BREAST CANCER</b> Lowering the age for screening for women aged 45-74, plus MRI scans for those with very dense breasts</p>	 <p>HPV testing for women aged 30 to 65, every 5 years or more, to detect <b>CERVICAL CANCER</b>, taking account of HPV vaccination status</p>	 <p>Frage testing for <b>COLORECTAL CANCER</b> in people aged 50 – 74 through faecal immunochemical testing (FIT) to determine follow up via endoscopy/colonoscopy</p>
 <p><b>LUNG CANCER</b> Testing for current heavy and ex-smokers aged 50-75</p>	 <p>Prostate specific antigen testing for <b>PROSTATE CANCER</b> in men up to 70, plus MRI scans for follow-up</p>	 <p>In places with high <b>GASTRIC CANCER</b> incidence and death rates, screening for Helicobacter pylori and surveillance of precancerous stomach lesions</p>

## European Commission Europe's Beating Cancer Plan<sup>3</sup> 2022

- **New recommendation:**  
**Lung Cancer Testing for current heavy and ex-smokers aged 50-75**



# CURRENT SITUATION OF LUNG CANCER IN SPAIN





# In Spain, more than 30,000 new cases of LC are diagnosed each year

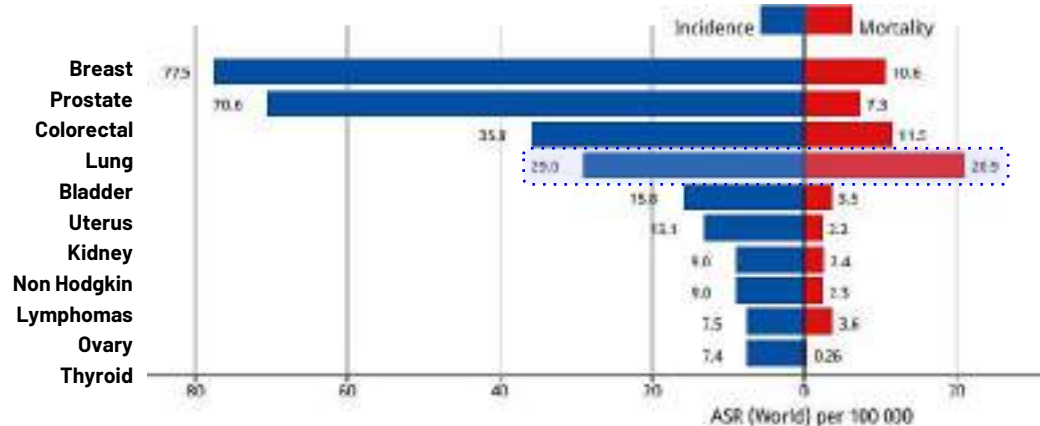


## Projections of the number of incident cases of cancer. Spain 2023

TIPO TUMORAL	N
Cavidad Oral y Faringe	7.852
Esófago	2.302
Estómago	6.932
Colon	28.465
Recto	14.256
Colorrectal	42.721
Hígado	6.695
Vesícula biliar	2.648
Páncreas	9.280
Laringe	3.378
Pulmón	31.282
Melanoma de piel	8.049
Riñón (sin pelvis)	8.626
Vejiga urinaria	21.694
Encéfalo y sistema nervioso	4.072
Tiroides	6.084
Linfoma de Hodgkin	1.539
Linfomas no hodgkinianos	9.943
Mieloma	3.082
Leucemias	6.411
Otros	18.046
Todos excepto piel no mel.	279.260



## Age-standardized incidence and mortality rates in Spain. Top 10 cancers<sup>2</sup>



Data source: Globocan 2020  
Graph production: Global Cancer Observatory (<http://gco.iarc.fr>)

**Mortality in LC represents 72% of incidence<sup>2</sup>**

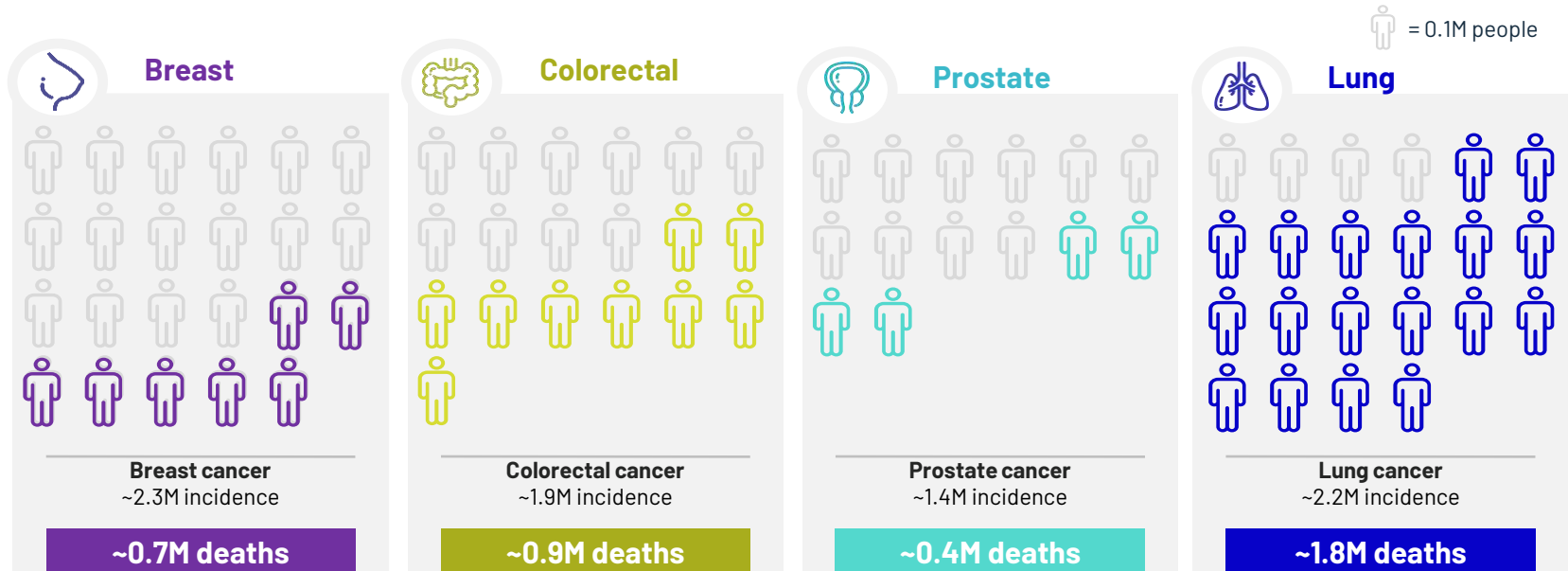
ASR: Age-standardized ; CP: cáncer de pulmón.

1. Red Española de Registros de Cáncer REDECAN. Estimaciones de la incidencia del cáncer en España, 2023. <https://redecan.org/es>; 2. Global Cancer Observatory, GLOBOCAN 2020. Disponible en: <http://gco.iarc.fr>.





# What does LC means in lives and costs?



**Deaths from LC exceed total deaths due to breast, colon and prostate cancer. LC accounts for 15% of all costs associated with cancer.**



# Why is mortality so high?<sup>1,2</sup>

## LC, health priority<sup>1</sup>



Cada **20 min**  
se pierde una vida  
por cáncer de pulmón  
en España



± **1,8 millones** de  
fallecidos en todo  
el mundo

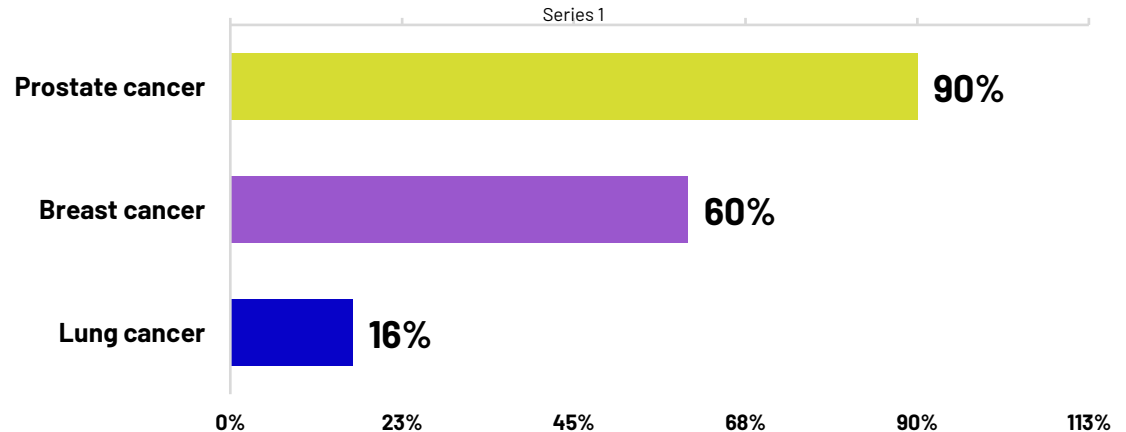


**80%** se  
diagnostica cuando  
ya se ha extendido



**1 de 6** pacientes  
sigue con vida cinco  
años tras el diagnóstico

## Percentage of cancers diagnosed BEFORE they spread<sup>2</sup>



**80% of LCs are diagnosed when they  
have already spread**

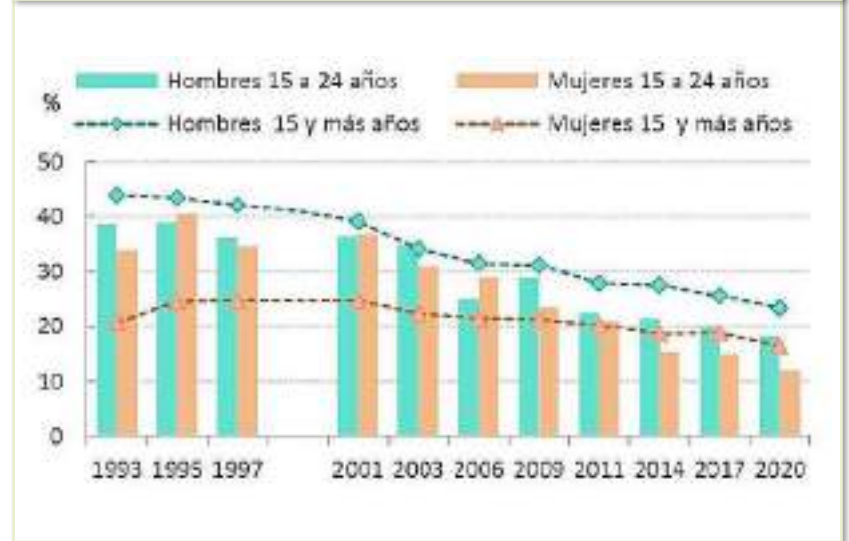


# Primary prevention in LC: do we smoke less?

In 2020, 19.8% of the population aged 15 and over reported smoking every day<sup>1</sup>



The decreasing trend observed over the years was confirmed (in 2014 it was 23% of the population)<sup>1</sup>



**Primary prevention is a necessary measure but with a medium/long-term effect**

1. Nota de prensa del Instituto Nacional de Estadística (INE), 26 de abril 2021: Encuesta Europea de Salud en España (EESE) Año 2020.



# WHAT HAVE WE DONE IN SPAIN?

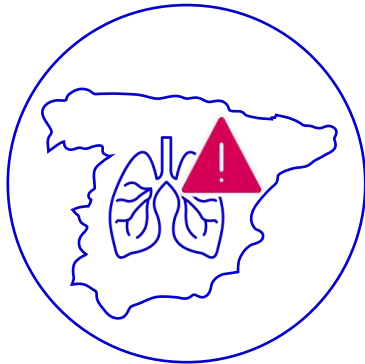




## Is LC screening a utopia in Spain?

**Spain, no early detection of lung cancer despite the fact that it kills 75 people a day**

*Dec. 12, 2019*



**NOMBRES**

Carolina Darias estudia la factibilidad de los programas de cribado de cáncer de pulmón

**Redacción**

15 de septiembre de 2021 (17:49 (UTC))



# LC screening programs in Spain



- 4 000 patients
- Age >40 yo
- IPA >10



- 8 000 patients
- Edad >40 yo
- IPA >15



- 1 500 patients
- Edad >55 yo
- IPA >30
- COPD and/or emphysema



- Prevalence of LC: 1,2%
- 610 patients

- Age: 55-79 years
- IPA smoker  $\geq 30$ ; ex-smoker (less than 15 years without smoking).
- Asymptomatic >50 years, smoker IPA 20 and any of these risk factors:
  - LC in first order relative.
  - Personal history of malignancy with >5 years disease-free.
  - Exposure to carcinogens (radon, asbestos, beryllium)
  - COPD or pulmonary fibrosis)



# Spain's position regarding LC screening<sup>1,2</sup>



RED ESPAÑOLA DE AGENCIAS DE EVALUACIÓN  
DE TECNOLOGÍAS Y PRESTACIONES DEL SISTEMA NACIONAL DE SALUD

## Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del Sistema Nacional de Salud - 2016<sup>1</sup>

False positives, overdiagnosis, and the costs  
of diagnostic evaluation made it advisable **not  
to implement this screening.**

## Estrategia en Cáncer del Sistema Nacional de Salud



## Estrategia en Cáncer del Sistema Nacional de Salud. Ministerio de Sanidad - 2021<sup>2</sup>

"overdiagnosis is estimated at a maximum of  
10% and false positives is much lower than in  
the NLST (...)."



## Spain's position regarding LC screening<sup>1,2</sup>



RED ESPAÑOLA DE AGENCIAS DE EVALUACIÓN  
DE TECNOLOGÍAS Y PRESTACIONES DEL SISTEMA NACIONAL DE SALUD

**Red Española de Agencias de Evaluación de  
Tecnologías y Prestaciones del Sistema Nacional  
de Salud - 2023<sup>1</sup>**

The cost-effectiveness analysis concluded that the screening program with LDCT represents improvements in health and also an additional cost compared to the alternative of not screening. However, **it is not a cost-effective option for the NHS, although, according to the scientific literature, it could be, in the smoking or ex-smoking population, especially when combined with prevention strategies consisting of smoking cessation programs.**

1. Cribado de cáncer de pulmón con Tomografía Computerizada de baja dosis. Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del SNS. Unidad de Asesoramiento Científico-técnico, avalia-t; 2016. Informes de Evaluación de Tecnologías Sanitarias. Disponible en: [https://avalia-t.sergas.es/DXerais/647/avalia-t201505\\_Cribado%20de%20ca%CC%81ncer%20de%20pulmo%CC%81n.pdf](https://avalia-t.sergas.es/DXerais/647/avalia-t201505_Cribado%20de%20ca%CC%81ncer%20de%20pulmo%CC%81n.pdf) (Último acceso mayo 2023); 2 Estrategia en Cáncer del Sistema Nacional de Salud. Ministerio de Sanidad. Disponible en: [https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/pdf/Estrategia\\_en\\_cancer\\_del\\_Sistema\\_Nacional\\_de\\_Salud\\_Actualizacion\\_2021.pdf](https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/pdf/Estrategia_en_cancer_del_Sistema_Nacional_de_Salud_Actualizacion_2021.pdf) (Último acceso mayo 2023).





# CASSANDRA PROJECT

*Cancer Screening Smoking Cessation AND Respiratory  
Assessment*



## Breaking through critical points

- Price
- Stigmatization and distress of a working-age population.
- Adherence
- Periodicity
- Do not reward smokers
- Evidence in a private medical setting



## Project developers



❖ Luis Seijo



❖ Juan Carlos Trujillo



## Questions



- Is our healthcare system ready for the implementation of LC screening?
- Is LC screening cost-effective?
- How should we select the cases to be screened?
- Are we doing all we can against smoking in Spain?



## CHALLENGES



Implementation **feasibility**



Complementary tests that help to detect possible patients



**Correct selection** of cases to be screened: risk modeling



Improvement of primary prevention



**Pilot Programs**

# Screening AND Smoking Cessation

## Screening AND Smoking Cessation

Screening en  
LC

Primary  
prevention



# Pilot project in Spain: CASSANDRA<sup>1</sup>



**Cassandra**  
Cancer Screening Smoking Cessation and Respiratory Assessment



# CASSANDRA and the patients







## Objetivos



**Patient-  
centered  
screening**



**Promoting  
respiratory  
health**

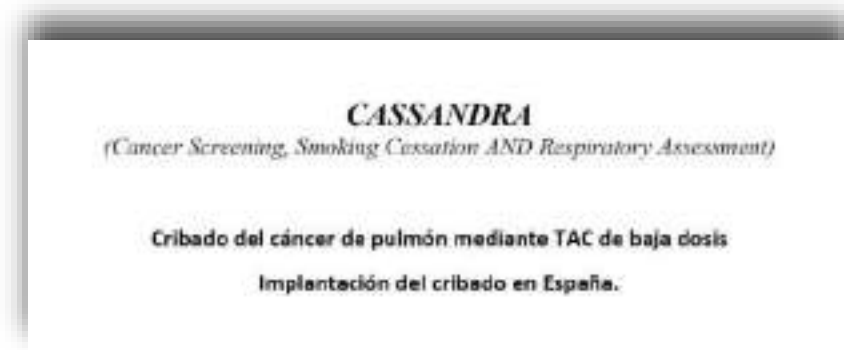


**Screening  
beyond  
cancer**



**·LDCT  
·Spirometry  
· Blood test**

# CASSANDRA: ACTION PROTOCOL



## Scientific comitee:

- Gorka Bastarrika
- Arantza Campo Ezquivela
- David Diaz Pérez
- Ingacio Muguruza Trueba
- Joan B. Soriano
- Jose Cervera
- Jessica González Gutiérrez
- Javier Zulueta Frances
- M<sup>a</sup> Teresa Perez Warnisher
- Juan Pablo de Torres Tajés
- Jaime Signes
- Carlos Jiménez



# Current status of Cassandra project



# CASSANDRA: BASIC NEEDS FOR SUCCESS

UNIQUE DATABASE



QUALITY CONTROL AND  
AUDIT



HOMOGENEOUS READING  
OF THE IMAGE



SEROTECA





40 hospitals

Cataluña	10
La Rioja	1
Comunidad de Madrid	7
Aragón	2
Comunitat Valenciana	3
Andalucía	6
País Vasco	1
Murcia	1
Castilla y León	2
Extremadura	1
Canarias	2
Navarra	1
Castilla la Mancha	1
Baleares	1
Galicia	0
Cantabria	1

## CASSANDRA HOSPITALS

- Inclusion Criteria
- No minimum number of cases in each center
- Prevalence of geographic representation
- Collaboration with Primary Care is CRUCIAL

### OBJECTIVE:

- To analyze inequity in access to health care.

#### Anexo I. Criterios de inclusión de los centros participantes

- \* Centro médico acreditado con equipo multidisciplinario que incluya, como mínimo:
  - Radiología
  - Neumología
  - Oncología Médica y Radioterápica
  - Anatomía Patológica
  - Cirugía torácica
  - Gestión de casos
- \* Unidad o comité de atención tabáquica

# CASSANDRA: DIFFUSION AND COMMUNICATION

[www.proyectocassandra.com](http://www.proyectocassandra.com)



The screenshot displays the website for the Cassandra project. At the top, there is a navigation menu with the following items: **GRUPO I+D+i**, **INICIATIVAS**, **ACTIVIDADES**, **INVESTIGACIÓN**, **INICIATIVA**, and **CONTACTO**. The main content area is titled "Bienvenidos" and "Participantes". Below the title, there is a map of Spain with several black location pins indicating the sites of the project. To the left of the map, the text reads: "Cribado del cáncer de pulmón mediante TC de baja dosis Proyecto piloto nacional". Below this, there is a paragraph of text: "La prevención es la clave para reducir la mortalidad. Un hombre solo tiene 10 minutos de vida para actuar y salvarse de un cáncer de pulmón. Si detectamos el cáncer en sus primeras etapas, el paciente tiene un 90% de posibilidades de sobrevivir. Tu tiempo de vida depende de ti. Actúa hoy mismo." At the bottom of the page, there is a dark blue banner with the text "Cribado del cáncer de pulmón mediante".

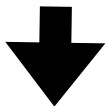
# CASSANDRA: DIFFUSION AND COMMUNICATION





# CASSANDRA: KEY POINTS

## UNANIMITY



- Unanimity of the scientific societies

## HOMOGENIZATION



- Single database with same variables
- External CRO
- Unique software

## SCENARIO



- Public health system
- Good geographic representation

## TOOLS FOR THE FUTURE



- Serotec
- Risk models
- Improved primary prevention

**Pilot project**



# The future of LC screening: risk models, biomarkers



# RISK MODELS: CASE SELECTION IMPROVEMENTS

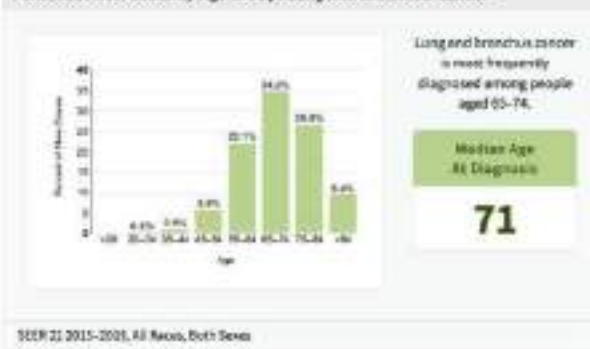
Susceptible population?

Risk factors?



15-30 times more prone to

Percent of New Cases by Age Group: Lung and Bronchus Cancer



over 60 years of age, there are more than 1,000 cases/100,000

## US Preventive Services Task Force (USPSTF)

### Screening for Lung Cancer US Preventive Services Task Force Recommendation State- ment

US Preventive Services Task Force

Article Information

**2013**

- 55 years in people with IPA  $\geq 30$   
would prevent 381 lung cancer  
deaths.

- Sensitivity 49%.

### Screening for Lung Cancer US Preventive Services Task Force Recommendation State- ment

US Preventive Services Task Force

Article Information

JAMA. 2021;325(10):962-969. doi:10.1001/jama.2021.1117

**2021**

- 50 to 80 years with IPA  $\geq 20$   
would prevent 503 lung  
cancer deaths.

- 65% sensitivity

**Evaluation of the Benefits and Harms of Lung Cancer Screening With Low-Dose Computed Tomography: A Collaborative Modeling Study for the U.S. Preventive Services Task Force**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
5600 Fishers Lane  
Rockville, MD 20857  
[www.ahrq.gov](http://www.ahrq.gov)

Contract No. HHS-A-290-2015-00011-J, Task Order No. 11

**Prepared by:**

Cancer Intervention and Surveillance Modeling Network (CISNET)  
Lung Cancer Working Group

AHRQ Publication No. 20-05266-EF-2  
March 2021

*Risk model–based screening strategies could result in higher benefits compared with risk factor–based screening strategies; however, the analysis did not consider issues of implementation and other potential challenges of risk model–based screening strategies*



## USPSTF2013 versus PLCOm2012 lung cancer screening eligibility criteria (International Lung Screening Trial): interim analysis of a prospective cohort study

Martin C Tammemägi, Marco Pirani, Alain Tammis, Renelle Myers, John Mayo, John Yin, Sekhinder Atkari Khattar, Ren Yuan, Sergio Cecconi, John English, Eric Bedard, Paul MacFarlane, Paul Barringer, Samer Hall, Qiaqi He, Henry Mariani, Jun Yang, Aydin Mirzaei, Linda Passos, Annette McWilliams, Fraser Burns, Kuan Pin Lin, Lin Ma, Stephanie Nielsen, Dawn Seftor, Mead Tiah, Vernon Steinhilber, Pieter van der Vliet, Louis Irving, Daniel Stehlfart, Mark McCusker, Diane Posso, Paul Fogarty, Emily Stone, David CE Lam, Ming-Yin Ng, Victor Vanchanchai, Christine G Beng, Rajwanj Hing, Sarah M Jones, Kuan Fong\*, Stephen Lam\*

Lancet Oncol 2022; 23:

PLCOm2012 appears to be more efficient to enrol into lung cancer screening programmes and should be included in these programmes.

### Added value of this study

This study provides prospective evidence based on a large multinational trial that shows that the PLCOm2012 model is significantly more sensitive at identifying those who will be diagnosed with lung cancer than the USPSTF2013 criteria and demonstrates that the cumulative potential life-years gained in individuals diagnosed with lung cancer was significantly greater in the group assigned to PLCOm2012 threshold of at least 1-70% at 6 years than in the group assigned to USPSTF2013 criteria. In addition, PLCOm2012 identified significantly more lung cancers in women than in men.

Compared to USPSTF2013-positive individuals, PLCOm2012-selected participants were older (mean age 65.7 years [SD 5.9] vs 63.3 years [5.7];  $p < 0.0001$ ), had more comorbidities (median 2 [IQR 1-3] vs 1 [1-2];  $p < 0.0001$ ), and shorter life expectancy (13.9 years [95% CI 12.8-14.9] vs 14.8 [13.6-16.0] years)

Review

## Lung Cancer Screening: New Perspective and Challenges in Europe

Jan P. Van Meerbeeck <sup>1</sup>, Emma O'Dowd <sup>2</sup>, Brian Ward <sup>3</sup>, Paul Van Schil <sup>4,5,6</sup> and Ansemiek Smeekx <sup>5,6</sup>

Cancers 2022, 14, 2343. <https://doi.org/10.3390/cancers14092343>

risk prediction models have been shown to be **superior** to selection using age and smoking status alone.

This may be due in part to these models **incorporating more detailed smoking data and considering other risk factors** such as chronic obstructive pulmonary disease (COPD) or asbestos exposure.

Currently, **there is no consensus on which model to use**, or even which threshold to use within a model

*Biomarkers?*

*Other risk factors?*

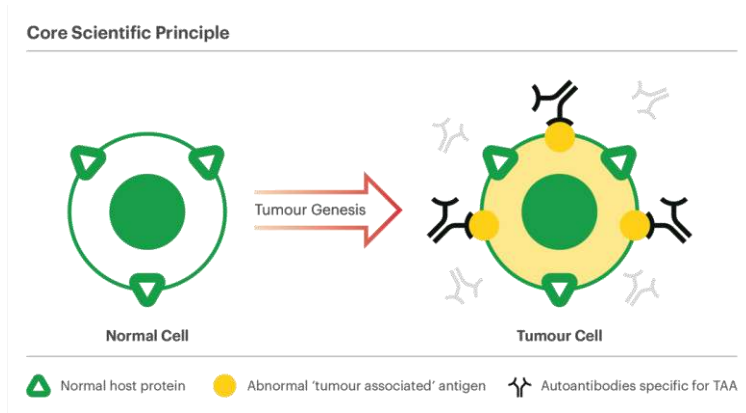
## Targets for biomarkers in LC screening

- Improvement of **selection criteria**
- Management of **indeterminate nodules**
- **Characterization of small nodules** beyond the reach of biopsy techniques
- Determination of **LDCT intervals**
- Patients with multiple nodules



# What do autoantibodies provide?

- Autoantibodies are produced early before the tumor is visible.
- They do not usually appear in healthy patients or appear at a low level.
- Patients with LC may have a specific "signature".



REVIEW ARTICLE



## Biomarkers in Lung Cancer Screening: Achievements, Promises, and Challenges



Luis M. Seijo, MD, PhD,<sup>a,b</sup> Nir Peled, MD, PhD,<sup>c</sup> Daniel Ajona, PhD,<sup>d,e,f,g</sup>  
Mattia Boeri, PhD,<sup>h</sup> John K. Field, PhD,<sup>i</sup> Gabriella Sozzi, PhD,<sup>j</sup> Ruben Pio, PhD,<sup>d,e,f,g</sup>  
Javier J. Zulueta, MD, PhD,<sup>k,l</sup> Avrum Spira, MD, MSc,<sup>l</sup> Pierre P. Massion, MD,<sup>m</sup>  
Peter J. Mazzone, MD, MPH,<sup>n</sup> Luis M. Montuenga, PhD<sup>d,e,f,g,\*</sup>

## Related projects in Spain

### **REFINE**

(**RE**gistry and **F**ollow up of  
**I**ndeterminate **N**odules using  
**E**arlyCDT)”

EarlyCDT-Lung

**Dagnostic Evaluation and Follow up of  
Indeterminate Nodules using EarlyCDT in Cataluña  
(**DEFINE.CAT**)**

To detect 7 autoantibodies in a blood test (P53, NY-ESO-1, CAGE, MAGE A4, GBU 4-5, SOX2, HuD) that our body produces in response to the presence of seven tumor antigens.



# CONCLUSIONS



- Lung cancer continues to be a serious problem
- Prevention alone is not the solution, SCREENING!
- Evidence in favor of screening is increasing
- EU pronunciation
- Spain has a previous experience in different Autonomous Communities, let's learn from it.
- Screening has room for improvement, but let it be born. Risk models, biomarkers...
- CASSANDRA, as an example of pilot project

***THANK YOU***

***ESKERRIK ASKO***