VII SIMPOSIUM
ICAPEM
Jerez de la Frontera
3 de noviembre 2022

Genetic Predisposition in Lung Cancer: Sex perspective

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Department of Medicine, University of Barcelona

Clínic Barcelona

IDIBAPS

Universitat de Barcelona

DISCLOSURES

- **Lectures and educational activities:**
  - Bristol-Myers Squibb, AstraZeneca, Roche, Takeda, Janssen
- **Consulting, advisory role:**
  - Roche, Takeda
- **Research Grants:**
  - Bristol-Myers Squibb, Boehringer Ingelheim, Amgen, Stilla, Inivata, AstraZeneca
- **Travel, Accommodations, Expenses:**
  - Bristol-Myers Squibb, Roche, Takeda, AstraZeneca, Janssen

OUTLINE

- Familial & Genetic susceptibility in Lung Cancer
- Cancer predisposition in Lung Cancer
- Sex perspective
- ICAPEM research, challenges & future
- Take home messages

OUTLINE

- **Familial & Genetic susceptibility in Lung Cancer**
- Cancer predisposition in Lung Cancer
- Sex perspective
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- Take home messages

LUNG CANCER risk factors (WHO)

Carcinogens, Group 1, WHO

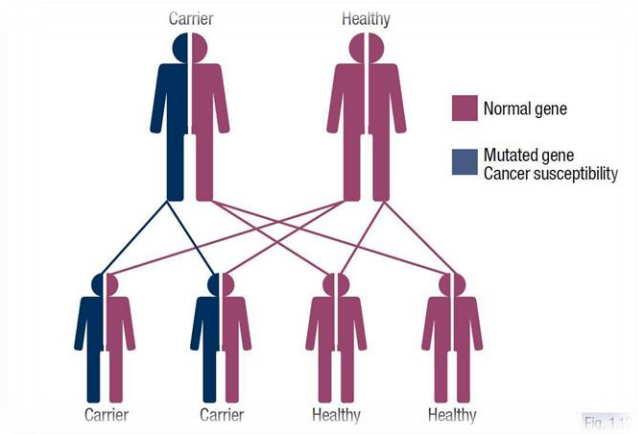
- Smoking
- Radon gas
- Asbestos
- Second-hand smoking
- Genetics
- Radiation
- Occupational
- Arsenic (H_20), diesel...

REALITY = misperception

TOBACCO Stigma minimizes the others

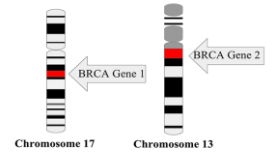
- Smoking
- Radon gas
- Asbestos
- Second-hand smoking
- Genetics
- Radiation
- Occupational
- Arsenic (H_20), diesel...

GENETICS: neglected risk factor in lung cancer

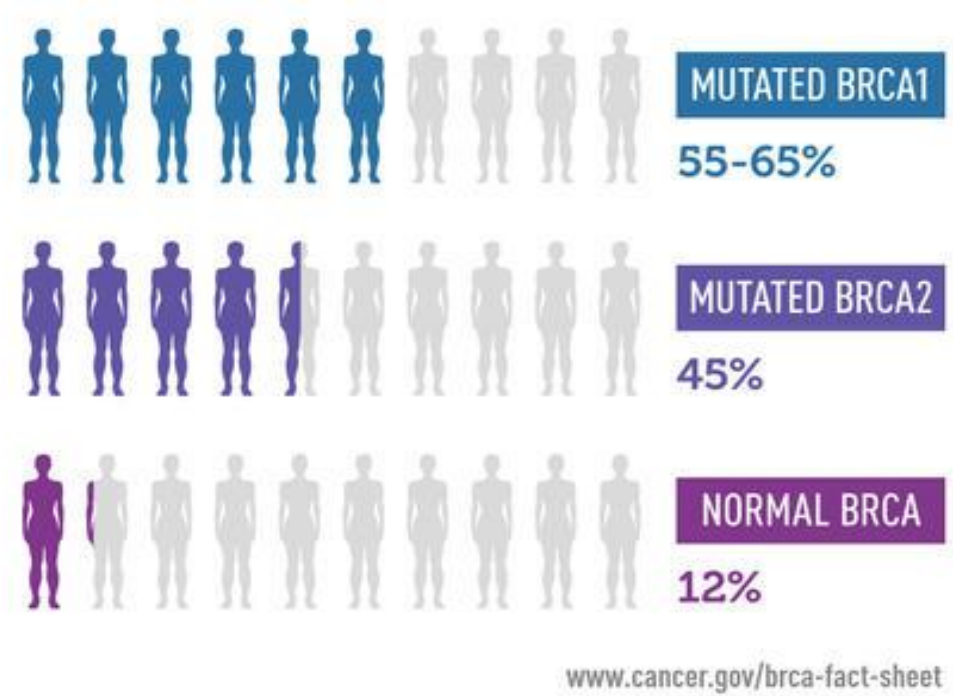


*"What is not **studied** is not reported, what is not **reported** does not exist & what does not **exist** is not prevented"*

GENETICS: neglected risk factor in lung cancer



Cancer Risk for Women Carrying *BRCA1/BRCA2* Mut.



Cancer Risk for other solid tumors

LUNG CANCER?

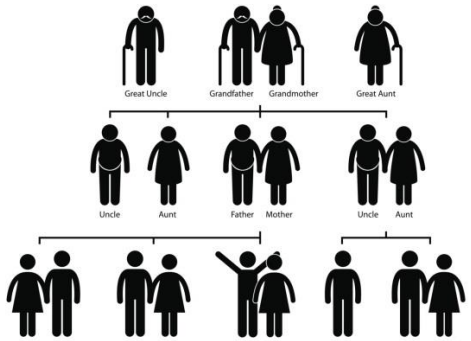
- Limited evidence
- No genetic assessment
- No criteria for study

NCI, cancer.gov; Momozawa, et al JAMA Oncol 2022

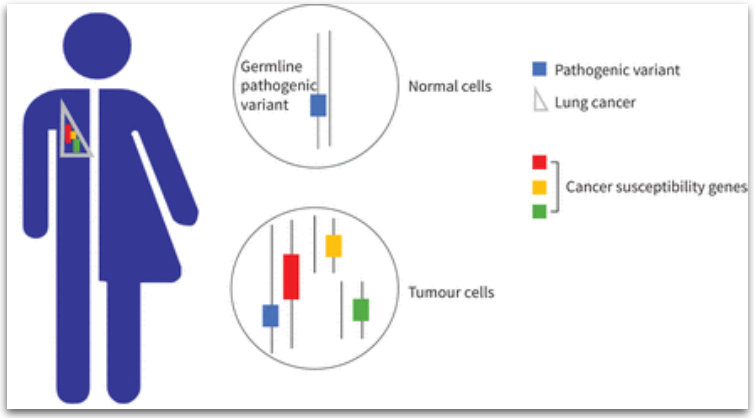
“Genetics” in patients with lung cancer

Genetic risk of Lung Cancer

FAMILIAL Susceptibility



GENETIC susceptibility



Parry EM et al J Thor Oncol 2017; Benusiglio PR et al, European Respiratory Review 2021

FAMILY HISTORY in Lung Cancer

- **RR for lung cancer = 2.36**
- **49,7-64%** of patients with lung cancer had family history of cancer
- **42,5% of female patients** with lung cancer had family history of cancer (mainly lung)

Family History of Cancer and Lung Cancer: information from the Thoracic Tumors Registry (TTR study)

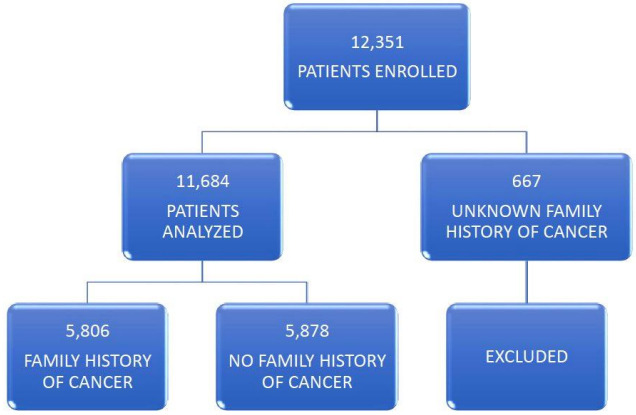
V. Calvo[1], E. Carcereny[2], D. Rodríguez-Abreu[3], R. López-Castro[4], M. Guirado[5], C. Camps[6], M. Cobo[7], A. L. Ortega[8], R. Bernabé[9], B. Massutí[10], J. Mosquera[11], E. Del Barco[12], J. L. González-Larriba[13], J. Bosch-Barrera[14], C. González Ojeda[15], M. Dómine[16], O. Juan[17], M. Martínez Cutillas[1], G. Benítez[3], A. Collazo-Lorduy[1], M. Cucurull[2], M. Provencio[1]

[1] Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; [2] Institut Català d'Oncologia Badalona, Hospital Universitari Germans Trias i Pujol, B-ARGO GROUP, Barcelona, Spain; [3] Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain; [4] Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [5] Hospital General Universitario de Elche, Alicante, Spain; [6] Hospital General Universitario de Valencia, Valencia, Spain; [7] Hospitales Universitarios Regional y Virgen de la Victoria, IBIMA, Málaga, Spain; [8] Hospital Universitario de Jaén, Jaén, Spain; [9] Hospital Universitario Virgen del Rocío, Sevilla, Spain; [10] Hospital General Universitario de Alicante, Alicante, Spain; [11] Hospital Universitario A Coruña, A Coruña, Spain; [12] Hospital Universitario de Salamanca, Salamanca, Spain; [13] Hospital Clínico San Carlos, Madrid, Spain; [14] Institut Català d'Oncologia, Girona, Spain; [15] Complexo Hospitalario Universitario de Vigo, Vigo, Spain; [16] Hospital Universitario Fundación Jiménez Díaz. IIS-FJD, Madrid, Spain; [17] Hospital Universitario La Fe, Valencia, Spain

IASLC | 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

V. Calvo, H. U. Puerta de Hierro Majadahonda, Madrid, Spain

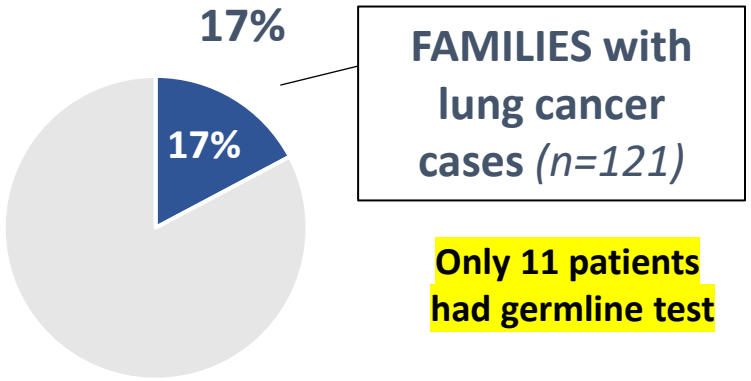
RESULTS



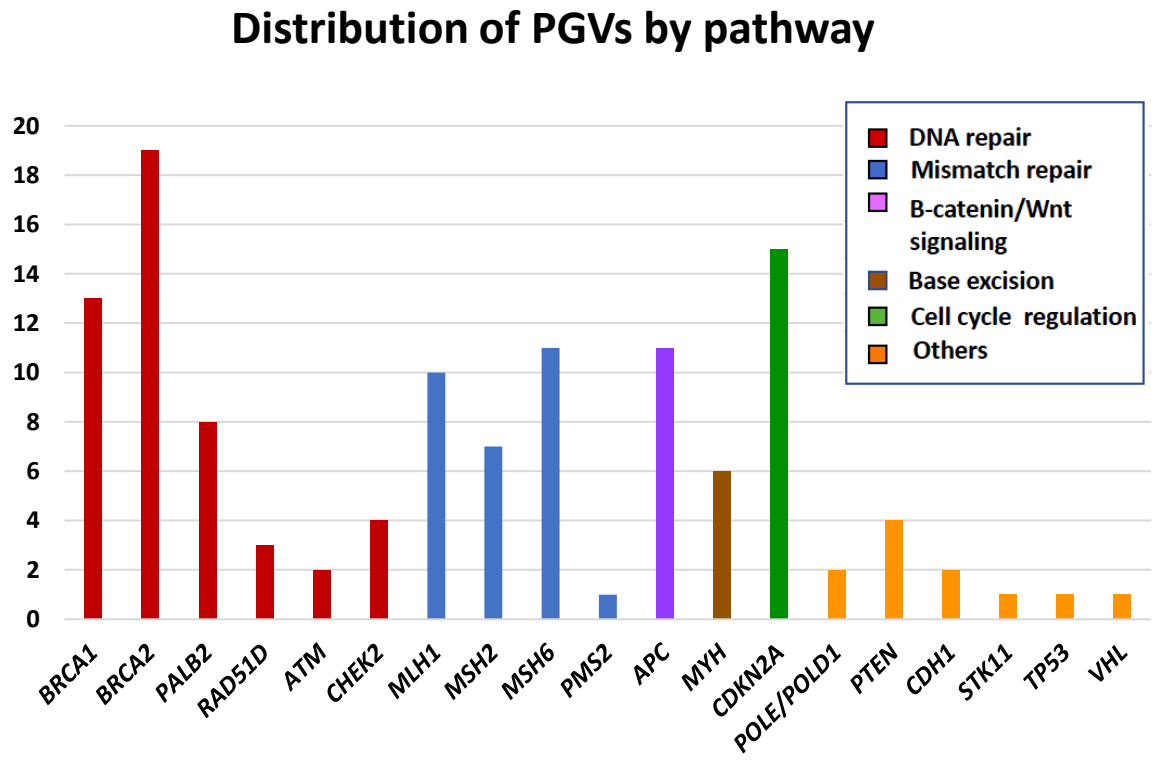
Sundquist, et al Int J Cancer. 2017;
Calvo V, et al. WCLC 2021;
Isla D, Anticancer Res. 2016.

FAMILIES with Cancer Predisposition Syndromes

Prevalence of Lung cancer in these families?



Only 11 patients had germline test



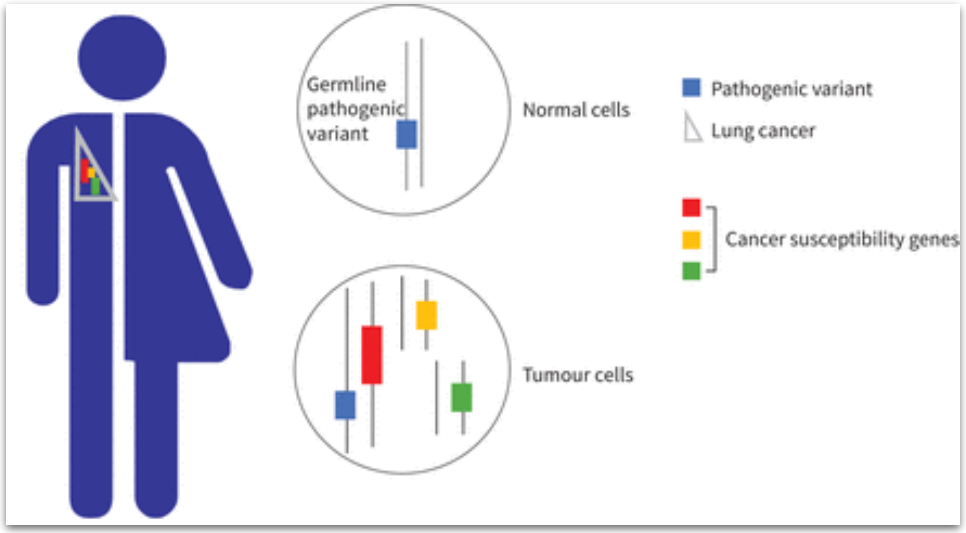
- **N=702 families harboring confirmed PGVs**
  - Genetic Counseling Unit, HCB
  - Period: Jan/2001 - Dec/2021
  - Personal/family history of lung cancer

Courtesy of Dr. Laguna

Laguna et al. ELCC, 2022

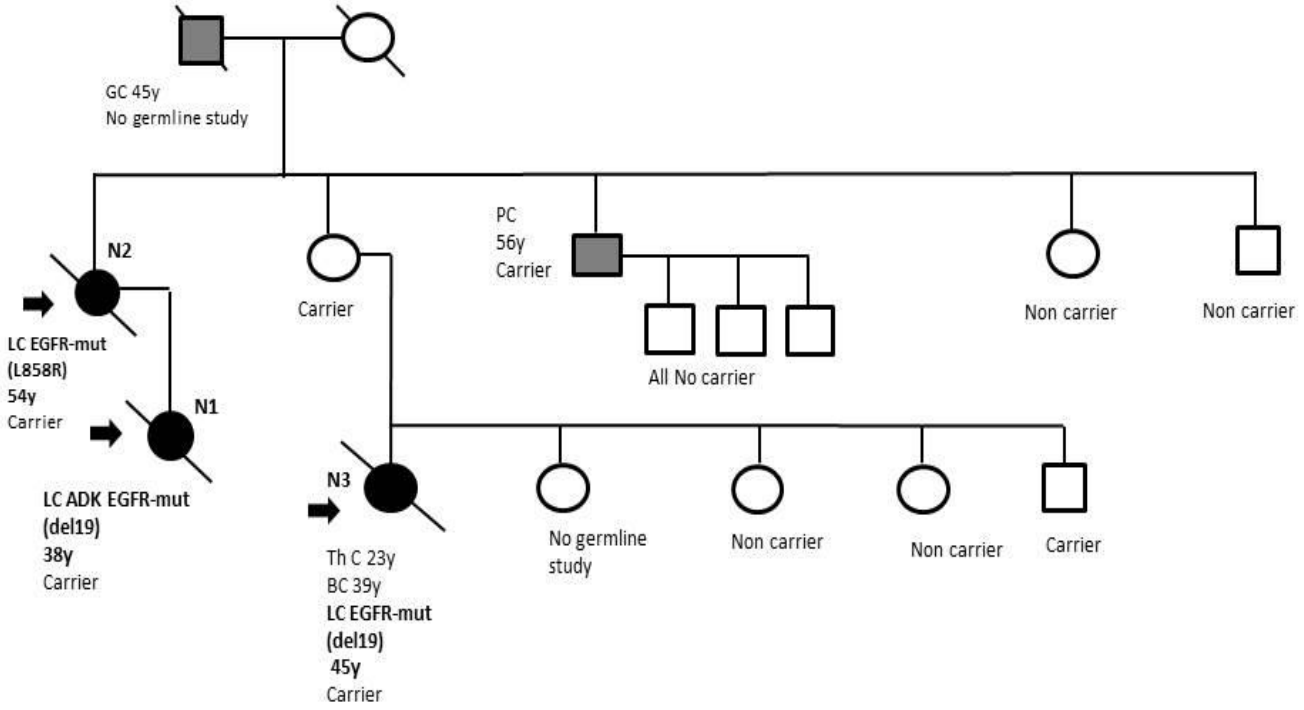
GENETICS: *Cancer predisposition genes*

Cancer Predisposition Genes



Benusiglio PR et al, European Respiratory Review 2021

LiFraumeni family



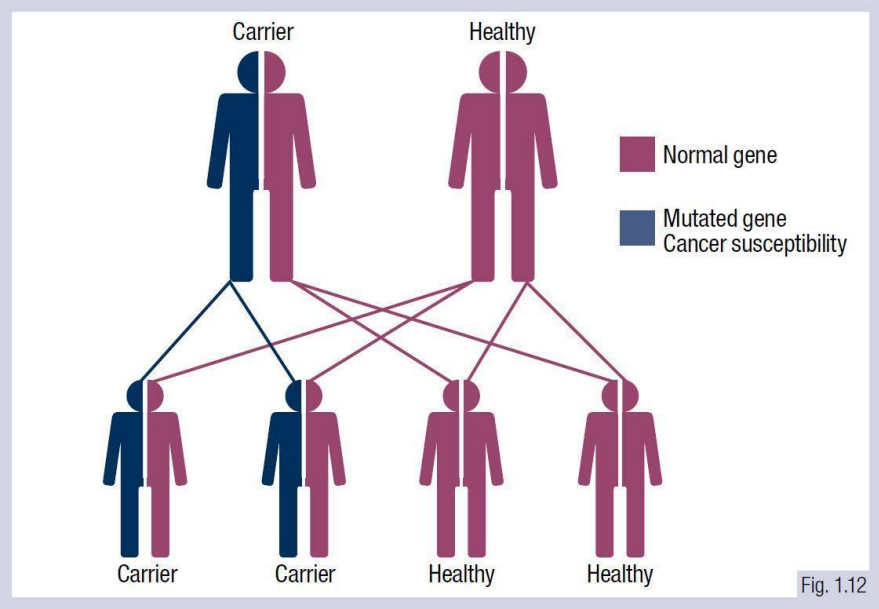
Mezquita, Jove et al, et al, J Thorac Oncol 2020

OUTLINE

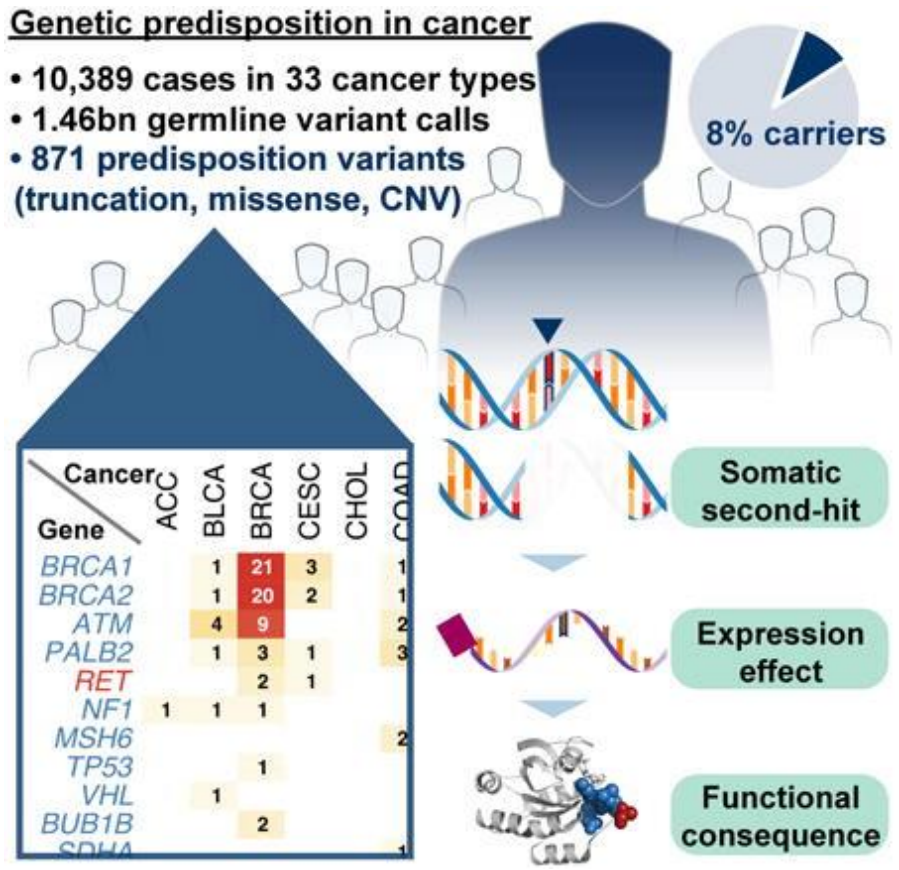
- Familial & Genetic susceptibility in Lung Cancer
- **Cancer predisposition in Lung Cancer**
- Sex perspective
- ICAPEM research, challenges & future
- Take home messages

Genetics in patients with solid tumors

Cancer predisposition genes



Inherited predisposition to cancer related to **pathogenic germline variants** (PGV) in cancer-predisposition genes

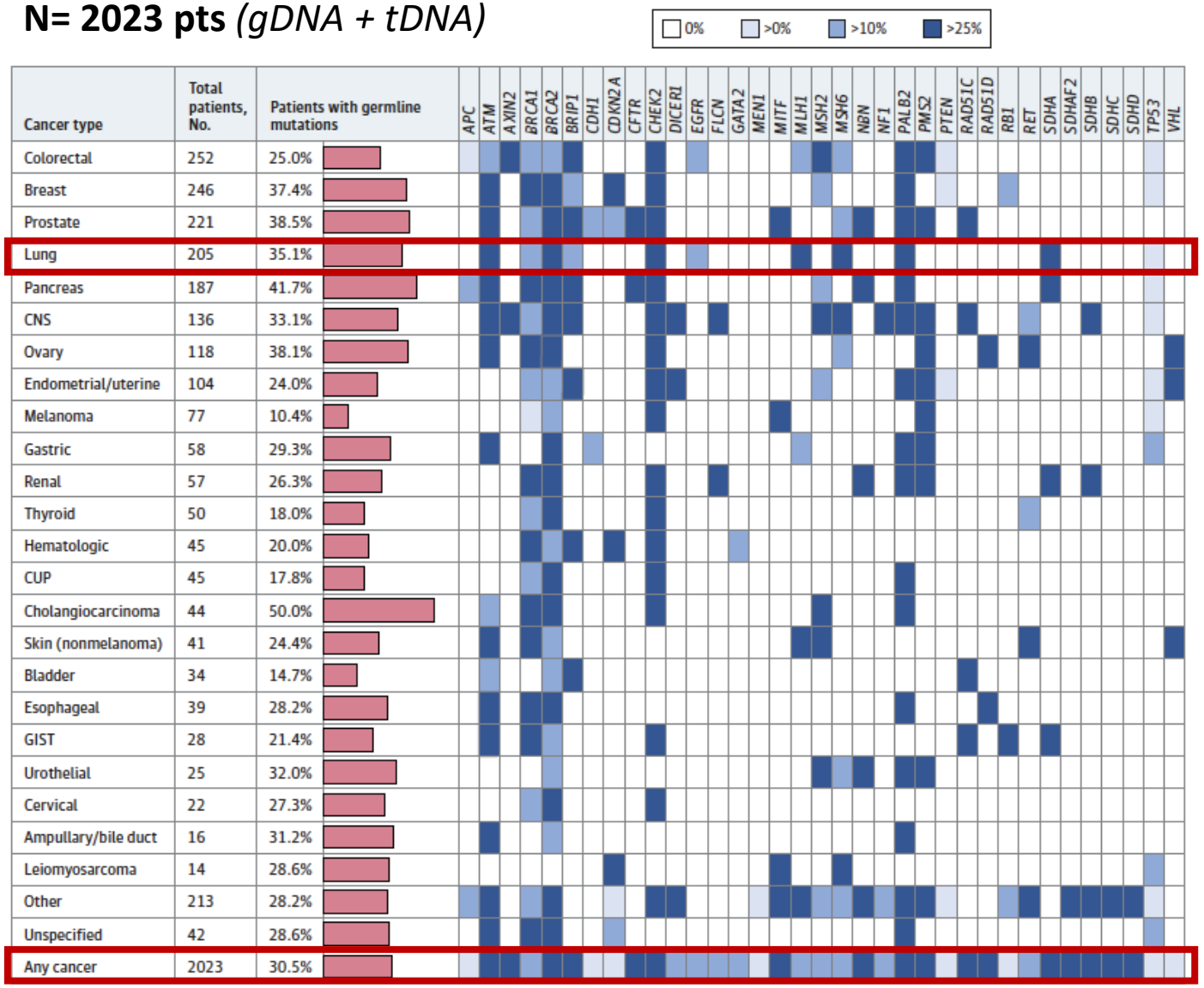


- **Shared** pathogenic variants & genes **across cancers**

Huang et al, Cell 2018

Pathogenic germline variants in Solid Tumors

N= 2023 pts *(gDNA + tDNA)*



Cancer type	Total patients, No.	Patients with germline mutations
Colorectal	252	25.0%
Breast	246	37.4%
Prostate	221	38.5%
Lung	205	35.1%
Pancreas	187	41.7%
CNS	136	33.1%
Ovary	118	38.1%
Endometrial/uterine	104	24.0%
Melanoma	77	10.4%
Gastric	58	29.3%
Renal	57	26.3%
Thyroid	50	18.0%
Hematologic	45	20.0%
CUP	45	17.8%
Cholangiocarcinoma	44	50.0%
Skin (nonmelanoma)	41	24.4%
Bladder	34	14.7%
Esophageal	39	28.2%
GIST	28	21.4%
Urothelial	25	32.0%
Cervical	22	27.3%
Ampullary/bile duct	16	31.2%
Leiomyosarcoma	14	28.6%
Other	213	28.2%
Unspecified	42	28.6%
Any cancer	2023	30.5%

Understimation in clinics
Identification of high-risk pop

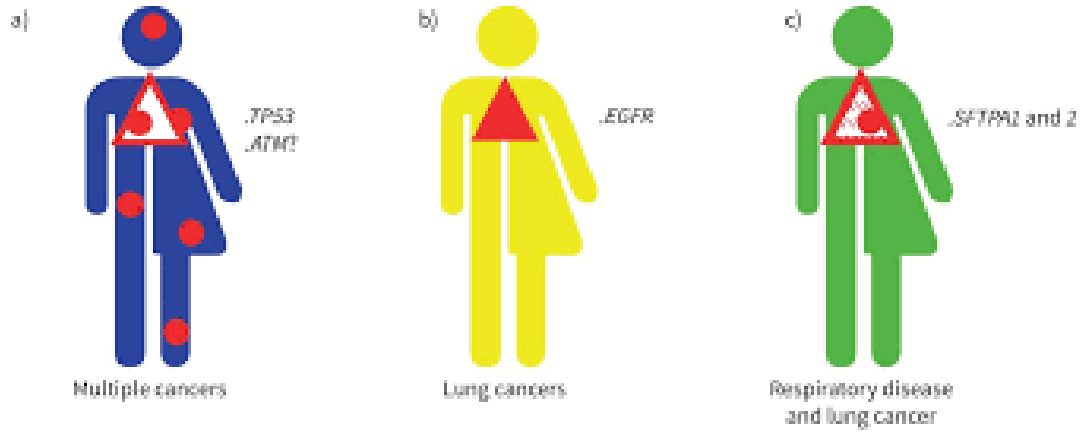
→ 20% PGV-carriers pts <u>did not meet criteria</u> for germline testing

→ 60% *TP53mut. carriers* did not meet Chompret criteria

Lincoln et al, JAMA Open Network 2020

Cancer Predisposition Genes in Lung cancer

Pathogenic germline variants in patient with cancer?



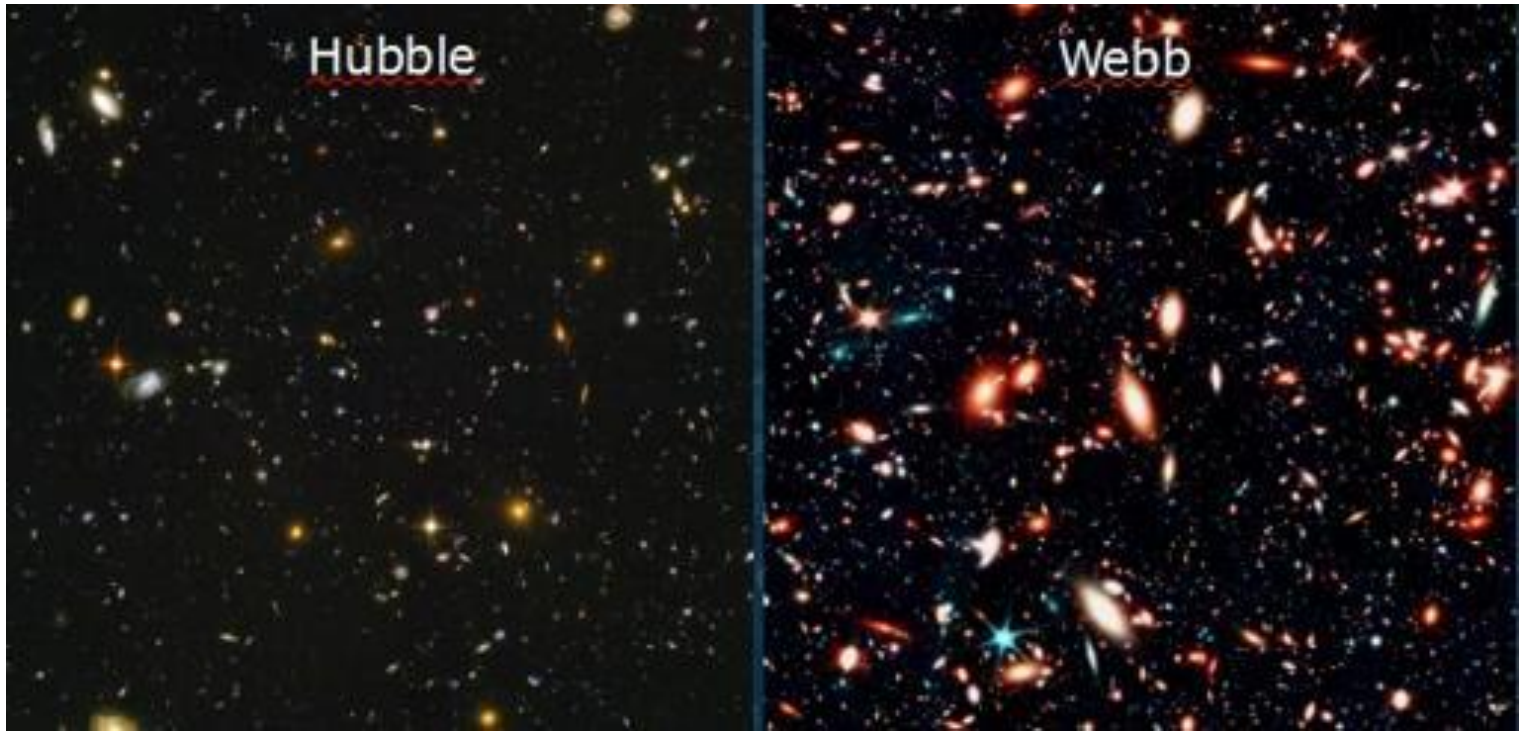
Benusiglio PR et al, European Respiratory Review 2021

LUNG CANCER?

- Limited evidence
- No criteria for study
  - N# of genes?
  - Type of genes/variants?
  - Interpretation

Cancer Predisposition Genes in Lung Cancer

Germline alteration analysis



Impact of the deep – coverage of the analysis

Cancer Predisposition Genes in Lung Cancer

Clínic Barcelona

Studying 8 cancer predisposition genes

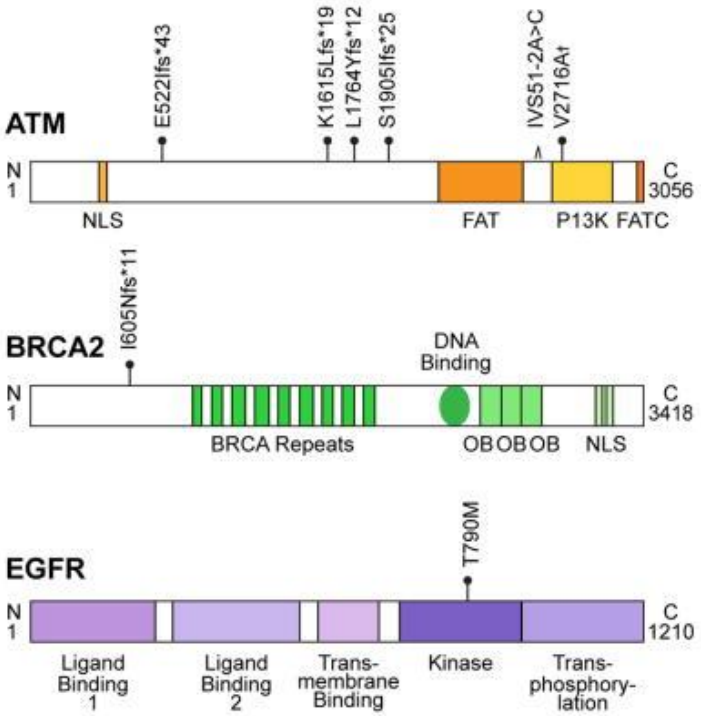
- **N=555 patients with lung adenocarcinoma**

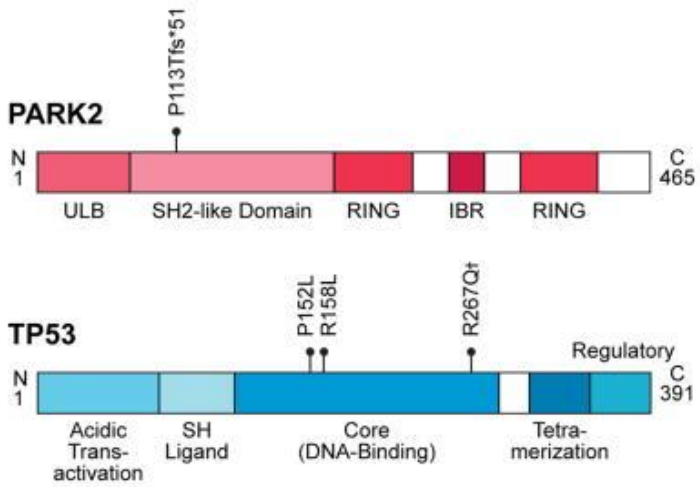
- **<u>2.5% with PGV</u>**

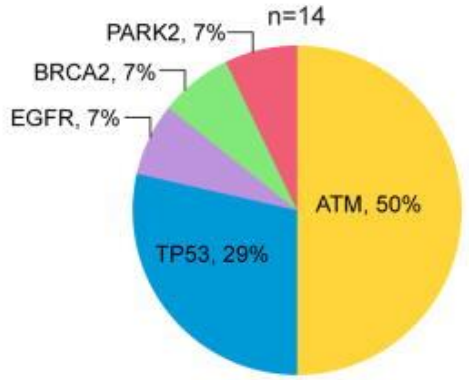
n= 14 PGVs in 5 cancer predisposition genes

- **Most common:**

- ***ATM (50%)***
- *TP53*
- *BRCA2*
- *EGFR*
- *PARK2*







Parry EM et al J Thor Oncol 2017

Cancer Predisposition Genes in Lung Cancer

Clínic Barcelona

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Studying 152 cancer predisposition genes

- **WES data from 134 pts with NSCLC**

- **15% of cases with PGVs** (152 genes)
- Most common: ***DNA repair pathways***

Cancer-Predisposing Genes in NSCLC

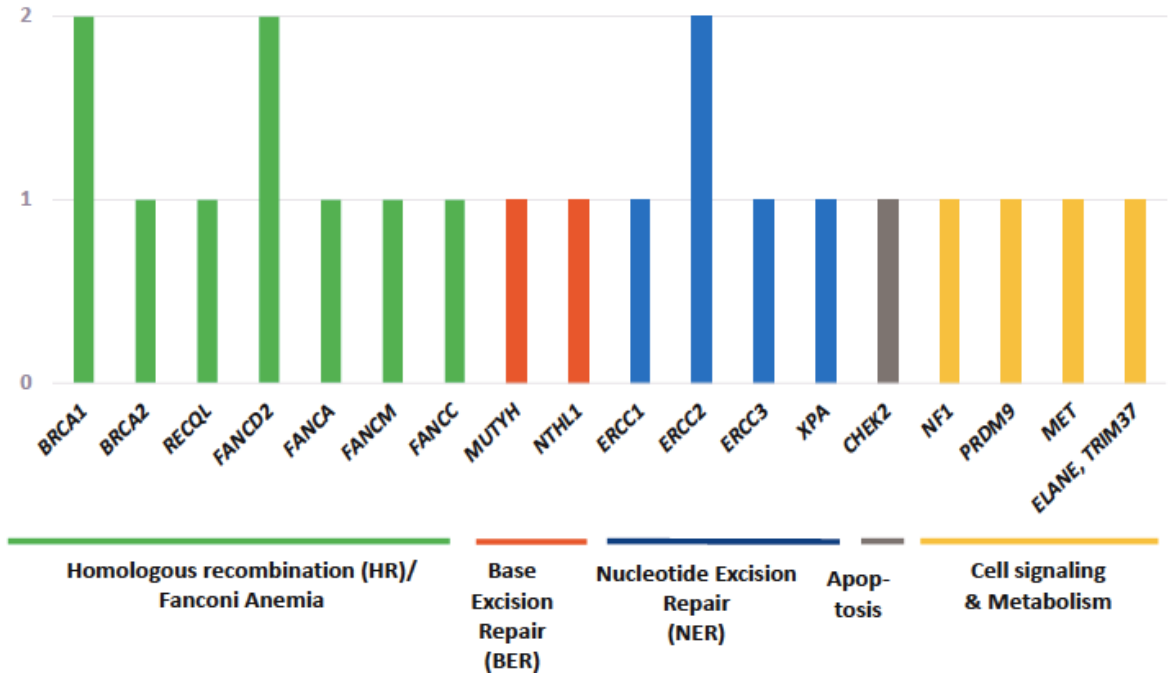
Prevalence of PGVs in lung cancer

15%

- **PGV in cancer-predisposing genes were found in 22 patients (15%);** 4 patients had additional somatic mutations (2) or LOHs (2) in the same genes

Figure 1. Prevalence of PGV in our study population

Distribution of PGVs by pathway

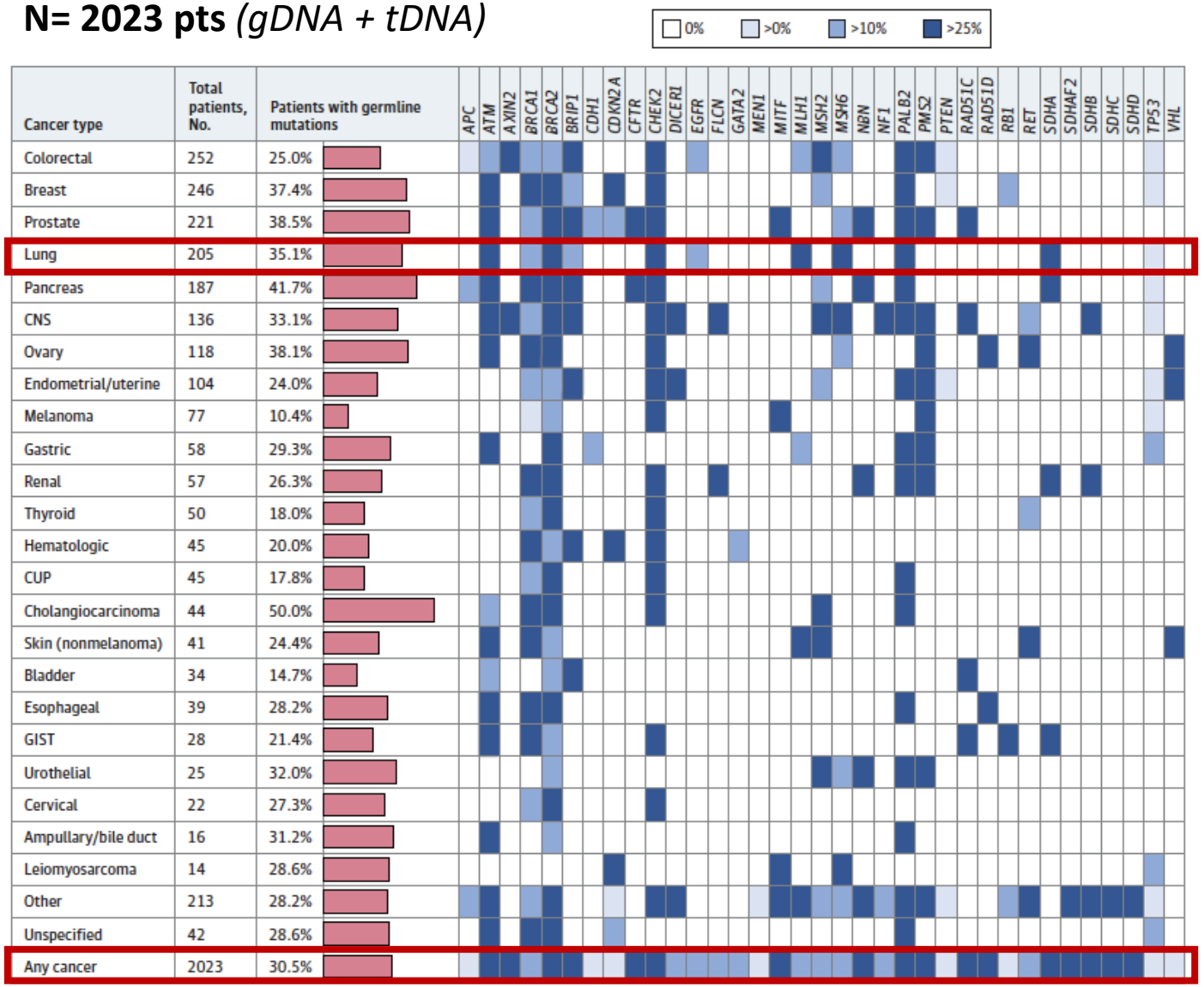


77% DNA repair pathways

Mezquita L, et al AACR 2021

Pathogenic germline variants in multitumor cohort

N= 2023 pts *(gDNA + tDNA)*



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APC ATM AXIN2 BRCA1 BRCA2 BRIP1 CDH1 CDKN2A CFTR CHEK2 DICER1 EGFR FLCN GATA2 MEN1 MITF MLH1 MSH2 MSH6 NBN NF1 PALB2 PMS2 PTEN RAD51C RAD51D RB1 RET SDHA SDHAF2 SDHB SDHC SDHD TP53 VHL

Studying % variable of cancer predisposition genes

31.5% of PGVs

Lincoln et al, JAMA Open Network 2020

Cancer Predisposition Genes in Lung Cancer

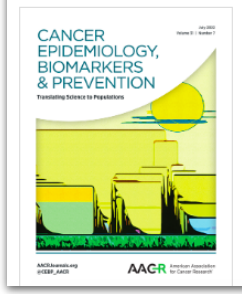
Clínic Barcelona

Studying 468 cancer genes

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COVID-19 WEBINARS

Volume 31, Issue 7
1 July 2022



RESEARCH ARTICLES | JULY 01 2022

Germline Pathogenic Variants Impact Clinicopathology of Advanced Lung Cancer

Semanti Mukherjee ; Chaitanya Bandlamudi; Matthew D. Hellmann ; Yelena Kemel ; Esther Drill ; Hira Rizvi; Kaitlyn Tkachuk; Aliya Khurram; Michael F. Walsh ; Marjorie G. Zauderer ; Diana Mandelker; Sabine Topka; Ahmet Zehir ; Preethi Srinivasan; Myvizhi Esai Selvan ; Maria I. Carlo ; Karen A. Cadoo; Alicia Latham ; Jada G. Hamilton ; Ying L. Liu ; Steven M. Lipkin ; Sami Belhadj ; Gareth L. Bond; Zeynep H. Gümüş ; Robert J. Klein ; Marc Ladanyi; David B. Solit ; Mark E. Robson ; David R. Jones ; Mark G. Kris; Joseph Vijai; Zsofia K. Stadler; Christopher I. Amos ; Barry S. Taylor ; Michael F. Berger; Charles M. Rudin ; Kenneth Offit

Check for updates

+ Author & Article Information

Cancer Epidemiol Biomarkers Prev (2022) 31 (7): 1450–1459.

https://doi.org/10.1158/1055-9965.EPI-21-1287 **Article history**

Results:

Germline PV in high/moderate-penetrance genes were observed in 222 (4.3%) patients; of these, 193 patients had PV in DNA damage repair (DDR) pathway genes including *BRCA2* (*n* = 54), *CHEK2* (*n* = 30), and *ATM* (*n* = *26*) that showed high rate of biallelic inactivation in tumors. *BRCA2* heterozygotes with lung adenocarcinoma were more likely to be never smokers and had improved survival compared with noncarriers. Fourteen patients with germline PV in lung cancer predisposing genes (*TP53, EGFR, BAP1,* and *MEN1*) were diagnosed at younger age compared with noncarriers, and of tumor suppressors, 75% demonstrated biallelic inactivation in tumors. A significantly higher proportion of germline PV in high/moderate-penetrance genes were detected in high-risk patients who had either a family history of any cancer, multiple primary tumors, or early age at diagnosis compared with unselected patients (10.5% vs. 4.1%; *P* = 1.7e−04).

4,3% with PGVs
N=222/5118 patients with aNSCLC

These data underscore the biological and clinical importance of germline mutations in highly penetrant DDR genes as a risk factor for lung cancer.

Impact:

The family members of lung cancer patients harboring PV in cancer predisposing genes should be referred for genetic counseling and may benefit from proactive surveillance

Mukherjee et al, Cancer Epidemiol Biomarkers Prev 2022

Cancer Predisposition Genes in Lung Cancer

Geographic - Ancestry differences?

Studying 1.021 cancer genes

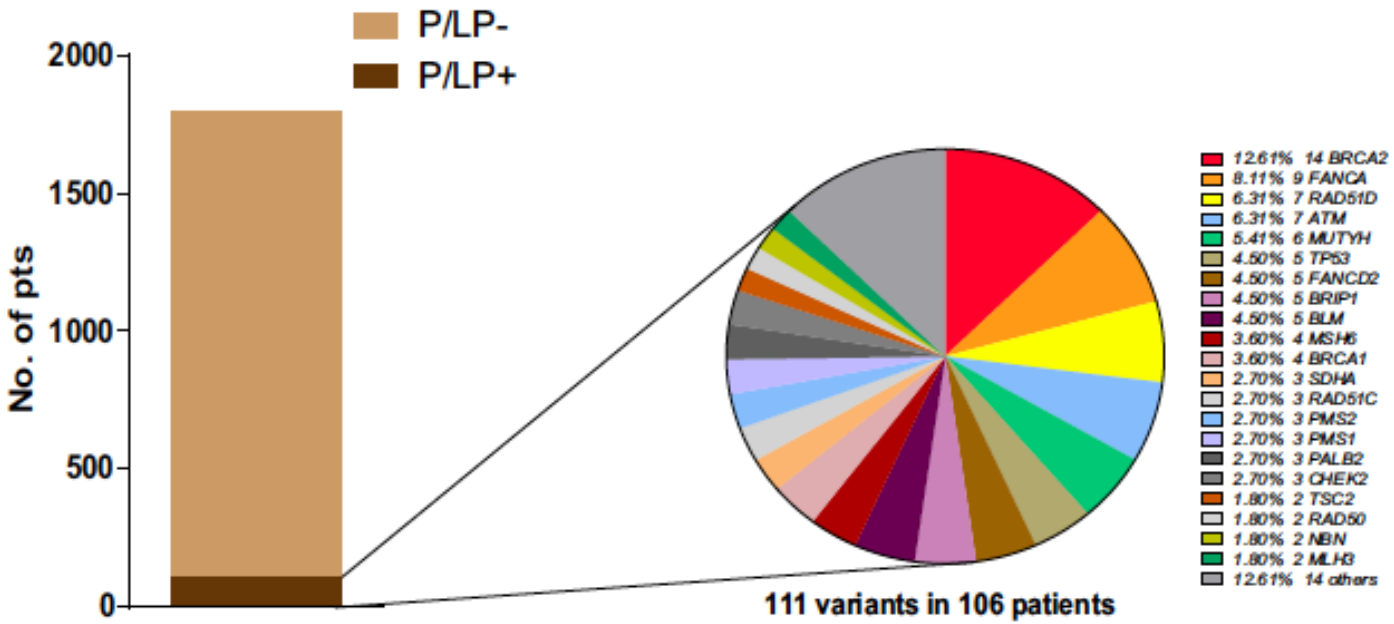
- **WES data from 1794 Asian pts with NSCLC**

- **<u>5,9% of cases</u> with PGVs**

- Most common: ***DNA repair pathways (BRCA2+++)***

- **Differences between Westerns vs Asian patients**

Chinese population



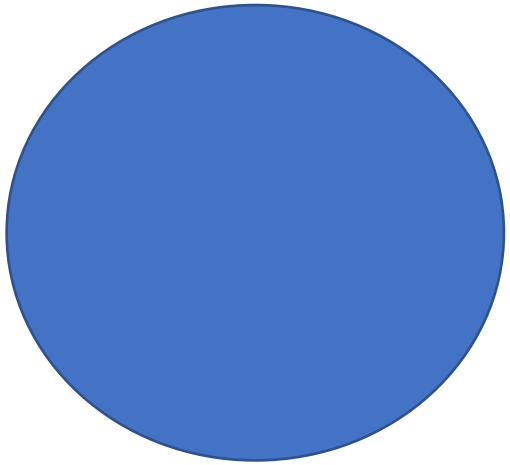
Peng W et al, Nature Communications 2022

OUTLINE

- Familial & Genetic susceptibility in Lung Cancer
- Cancer predisposition in Lung Cancer
- **Sex perspective**
- ICAPEM research, challenges & future
- Take home messages

Lung cancer is not an unique disease

Classically



Oncologist

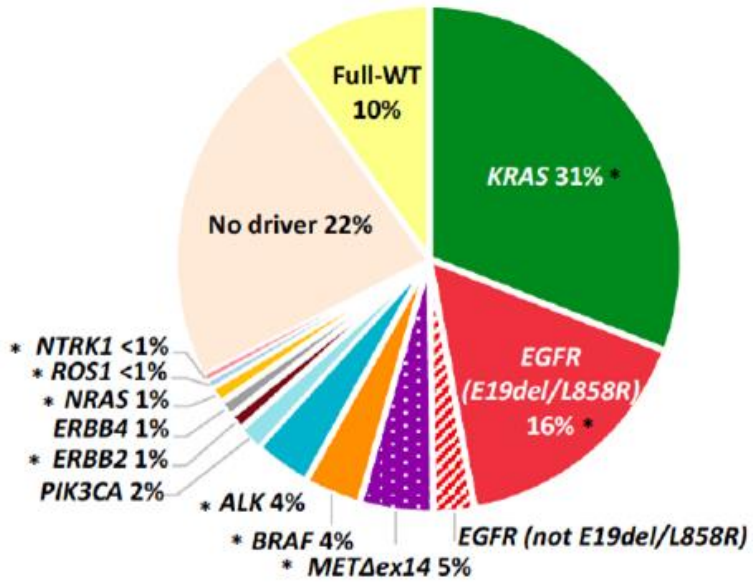
Different subpopulations

- **Clinical profile**
- **Treatments**
- **Prognosis**

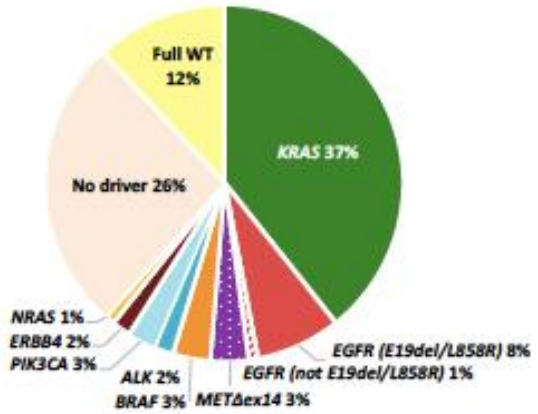
Molecular profile of Lung cancer

Hospital Clinic, NSCLC

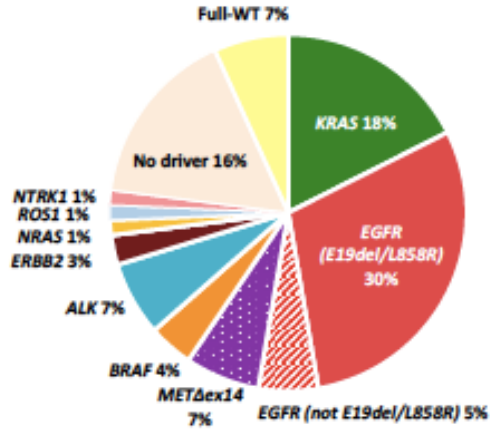
Overall pop



MALE



FEMALE



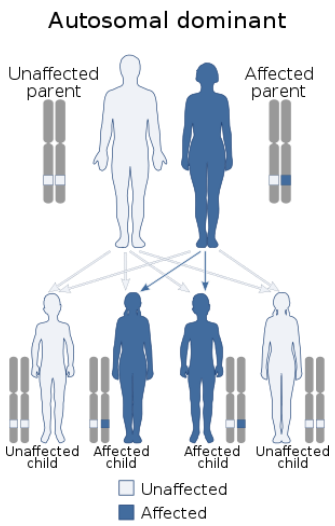
Marin E et al, Cancers 2020

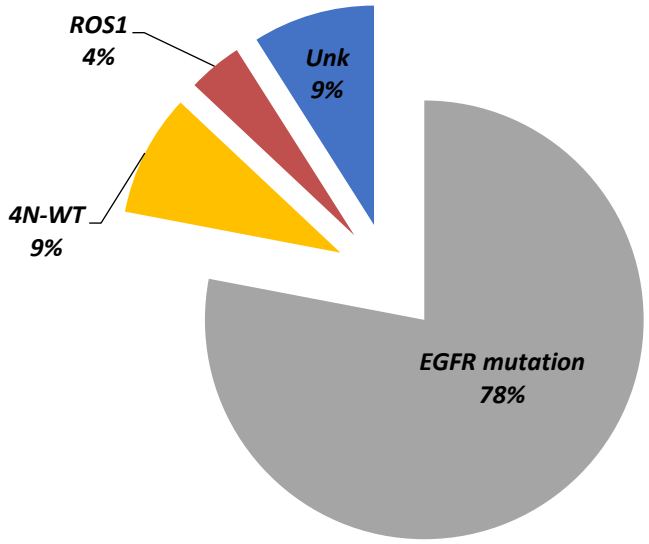
Differences on % of driver oncogenic alterations

Clinical profile in PGVs-carriers

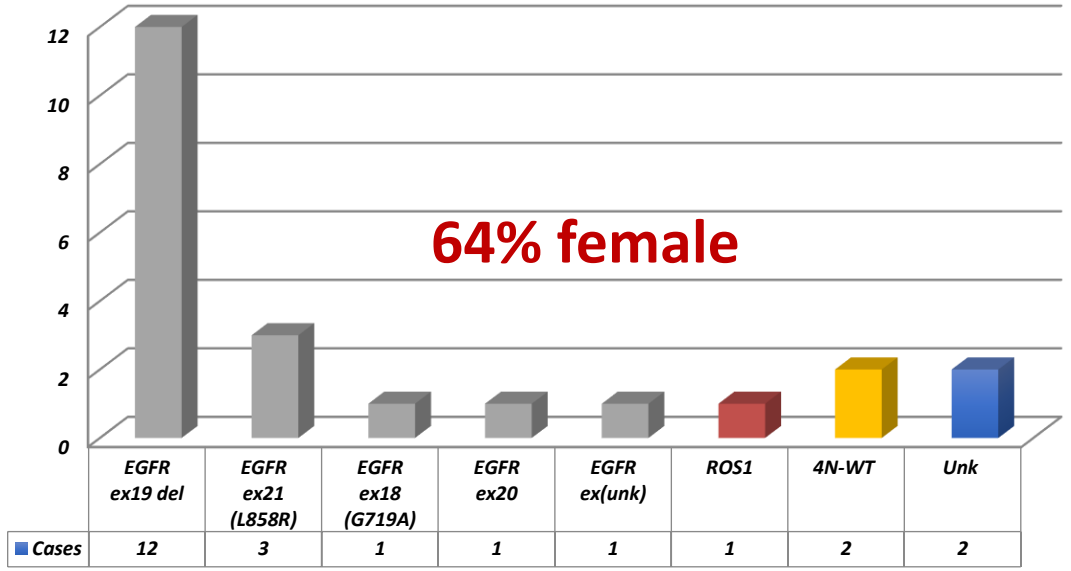
90% LiFraumeni patients with lung cancer (19/21) with somatic oncogenic driver alt.

Germline
***TP53* mut**

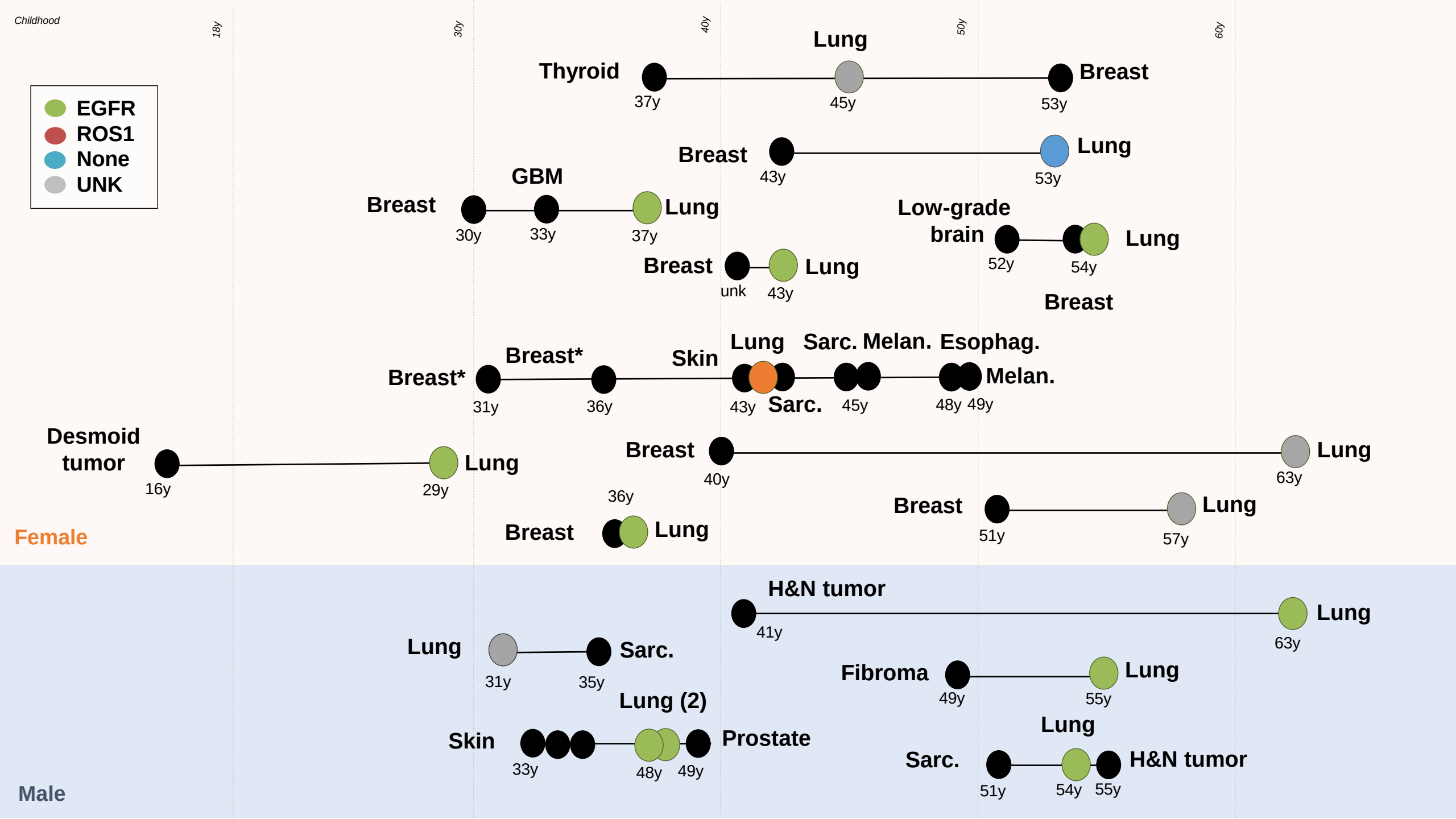




4N: four negative (*EGFR* and *BRAF* wildtype, *ALK* and *ROS1* not rearranged)



Mezquita, Jove et al, et al, J Thorac Oncol 2020


Childhood
18y
30y
40y
50y
60y
EGFR
ROS1
None
UNK
Thyroid
37y
Lung
45y
Breast
53y
Breast
43y
Lung
53y
GBM
Breast
30y
33y
Lung
37y
Low-grade brain
52y
Lung
54y
Breast
unk
43y
Lung
Breast
Breast*
31y
Breast*
36y
Skin
43y
Lung
Sarc.
45y
Sarc.
Melan.
48y
Esophag.
49y
Melan.
Desmoid tumor
16y
Lung
29y
Breast
40y
Lung
63y
36y
Breast
Lung
Breast
51y
Lung
57y
Female
H&N tumor
41y
Lung
63y
Lung
31y
Sarc.
35y
Fibroma
49y
Lung
55y
Lung (2)
Skin
33y
48y
49y
Prostate
Lung
Sarc.
51y
54y
55y
H&N tumor
Male

Profile of patients with pathogenic germline variants

PGVs is associated with any specific MOLECULAR PROFILE in lung cancer?

Other PGVs
(non-TP53)

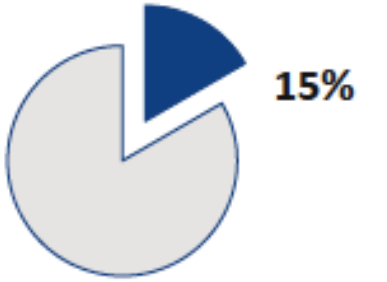


Figure 1. Prevalence of PGV in our study population

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

- In the 22 PGV-carriers, **68% had a somatic oncogene-driven alteration** (15/22)

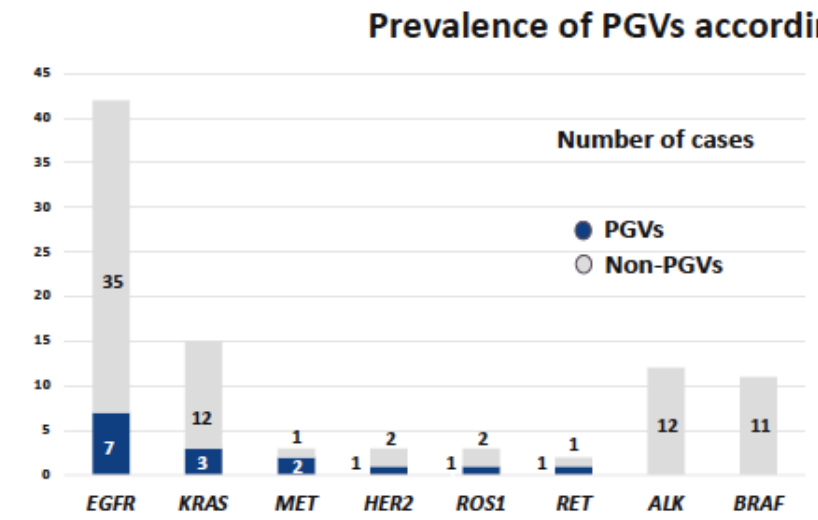


Figure 4. Frequency (N) of PGVs in each molecular group

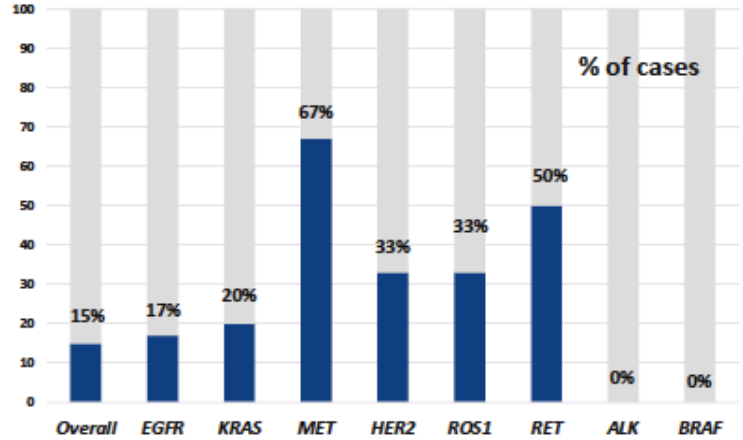


Figure 5. Frequency (%) of PGVs in each molecular group

55% were female

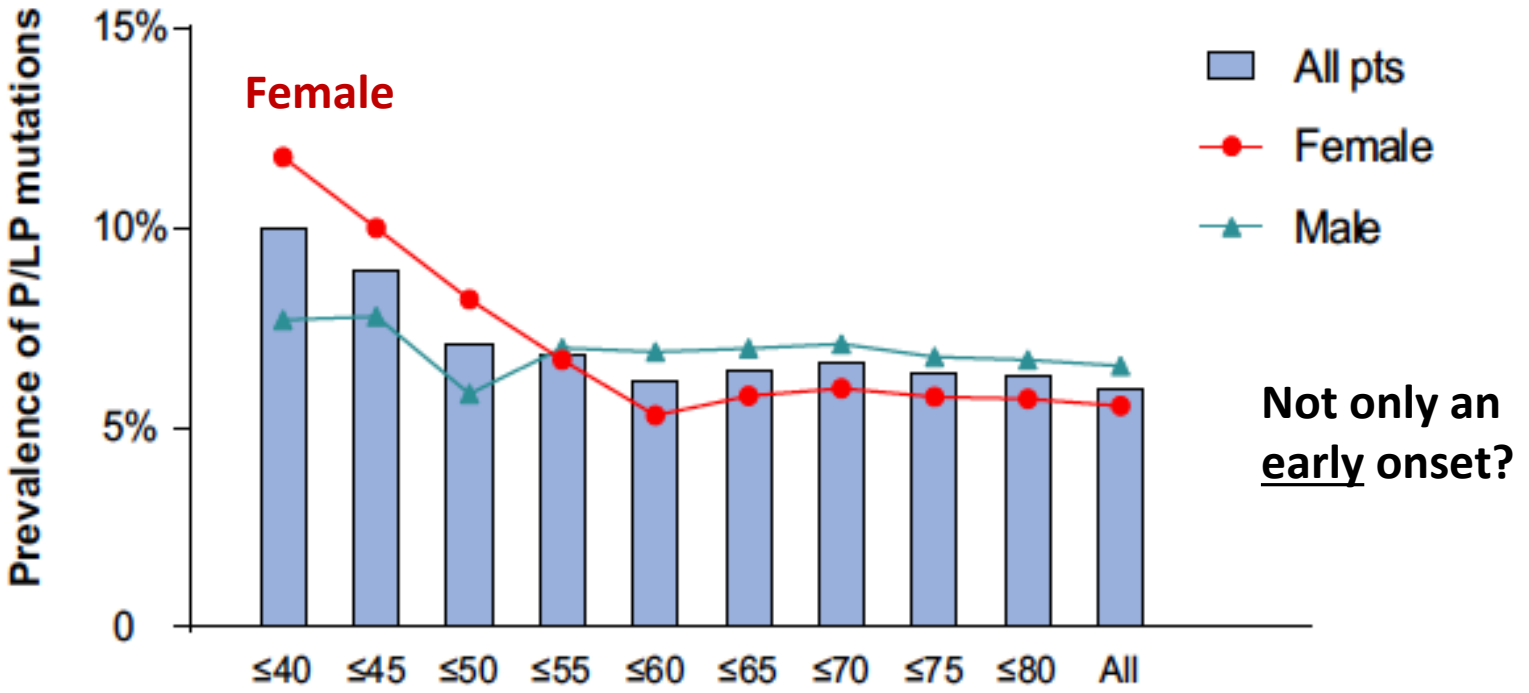
Mezquita L, et al, AACR 2021

Clinical profile in PGVs-carriers

PGVs is associated with any specific PROFILE in lung cancer?

Asian patients, with lung cancer
PGVs-carriers

b



Not only an early onset?

c

Peng W et al, Nature Communications 2022

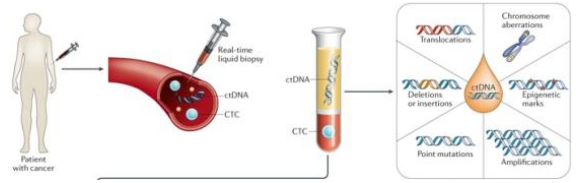
PGVs detection In NSCLC by ctDNA-liquid biopsy

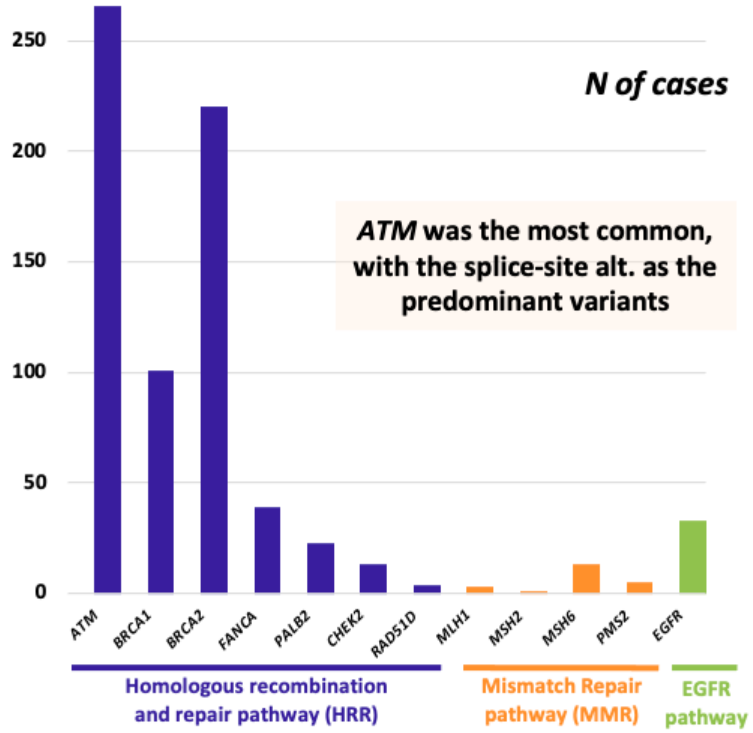
- **Liquid biopsy NGS** = incidental PGVs
- **~ 2.3% of pts** (n=31,126) with NSCLC harboring PGVs (47% with driver alt)

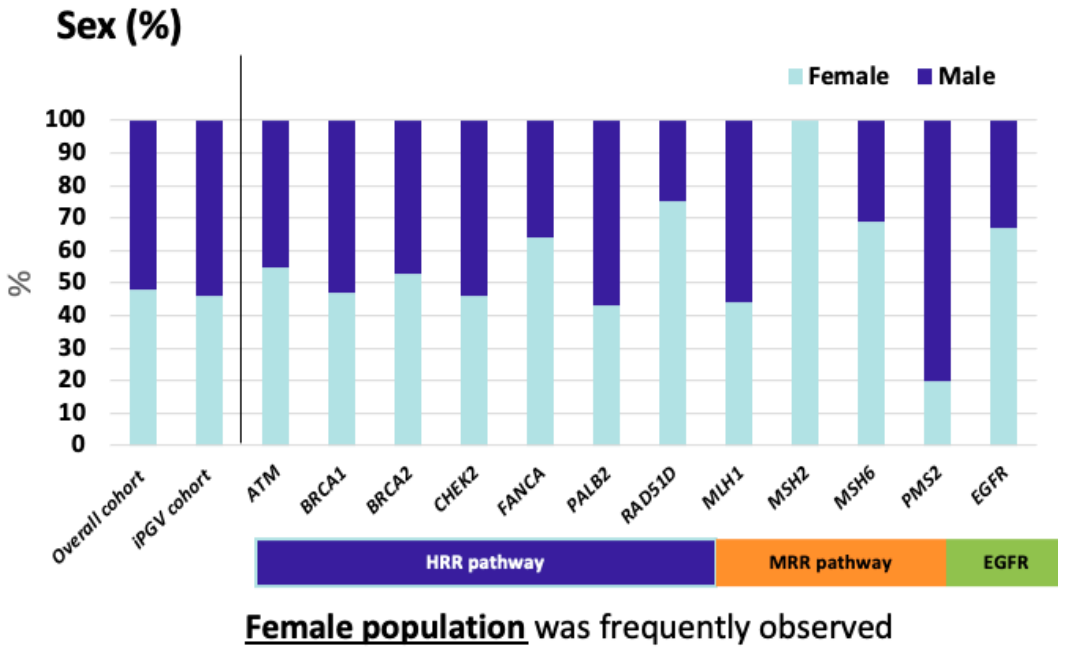
54% female

	Overall Population, N=31126	Population with iPGVs, N=721
Age		
≥50 years, Range	29733 (96%) 15-104	683 (95%) 22-100
Sex		
Male	14990 (48%)	334 (46%)
Female	16136 (52%)	387 (54%)
Histology		
Adenocarcinoma	24029 (77%)	582 (80%)
Squamous	4945 (16%)	102 (14%)
Others	2152 (7%)	37 (6%)

Studying 12 Cancer predisposition genes







Female population was frequently observed

Mezquita L et al, ASCO 2022,
Mezquita L et al, WCLC 2022

OUTLINE

- Familial & Genetic susceptibility in Lung Cancer
- Cancer predisposition in Lung Cancer
- Sex perspective
- **ICAPEM research, challenges & future**
- Take home messages

ICAPEM project: INHERITY

ICAPEM
ASOCIACIÓN PARA LA INVESTIGACIÓN DEL CÁNCER DE PULMÓN EN MUJERES

Clínic Barcelona

Studying 61 cancer genes

- **Prospective study of pts with NSCLC**
- **N> 120, n=55 preliminary analysis**

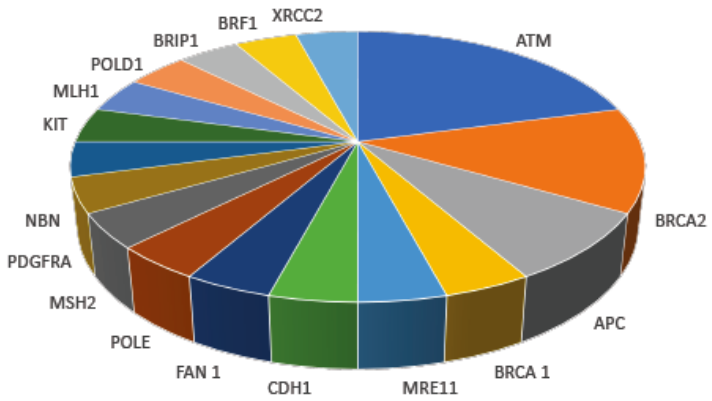
- **Objective:**
- Prevalence by sex
- Clinical/molecular profile: criteria for clinical genetics

53% female

Characteristics	Total population N = 55	Patients with germline variants N=19
Age, median (range)	57 (39,84)	58 (39,75)
≤ 45 years	12 (22%)	2 (11%)
≤ 60 years	33 (60%)	7 (37%)
Gender, n (%)		
Male	24 (44%)	9 (47%)
Female	31 (56%)	10 (53%)
Race , n (%)		
Caucasian	52 (95%)	19 (100%)
Asian	2 (4%)	0 (0%)
African	1 (2%)	0 (0%)
Smoking status, n (%)		
Never	21 (38%)	5 (26%)
Former	34 (62%)	14 (74%)
≤15 pack-years	7 (13%)	5 (26%)
>15 pack-years	27 (49%)	9 (47%)
Histological type, n (%)		
Adenocarcinoma	46 (84%)	15 (79%)
Squamous	6 (11%)	3 (16%)
Adenosquamous	1 (2%)	0 (0%)
Large cell	2(4%)	1 (5%)
Somatic actionable mutations, n (%)	28 (51%)	9 (47%)
EGFR	16 (29%)	6 (21%)
ALK	10 (18%)	3 (16%)
ROS-1	2 (4%)	0 (0%)

34,5% with PGVs

Mainly in DDR pathways



Criteria for inclusion:

- Selection criteria:

1) familiar history of lung cancer: one first-degree relative, or two or more second-degree relatives with NSCLC regardless of age; or
2) age and negative or low tobacco exposure: diagnose ≤ 45 years or ≤ 60 years with a pack-years index ≤ 15; or
3) presence of somatic actionable mutations in the tumor biopsy

Principal investigators: *Dr. Lastra, Prof. Isla*

Zurera et al, ESMO 2022

SCAN study

Observational prospective study

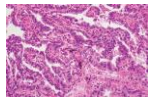
INCLUSION CRITERIA

- ✓ **NSCLC patients:**
  - new diagnosis
  - under therapy
  - under follow-up
  - Survivors
- ✓ **Molecular profile available (NGS)**

N=500

Personal and family CANCER history

Environmental & occupational factors



MOLECULAR PROFILE

N=250 patients enrolled

*** Study Young investigator:**
Juan Carlos Laguna, MD
*** Study Senior investigator:**
Laura Mezquita MD, PhD

- **Primary endpoint:** Correlation between family/cancer history & molecular profile
- **Secondary endpoints:**

- Identification of high-risk population for genetics counseling
- Establish hypothesis on environmental-genetic interaction in pts with lung cancer

Challenge n#1: Identify the carriers in lung cancer

Any data in <u>other lung cancer</u> types?

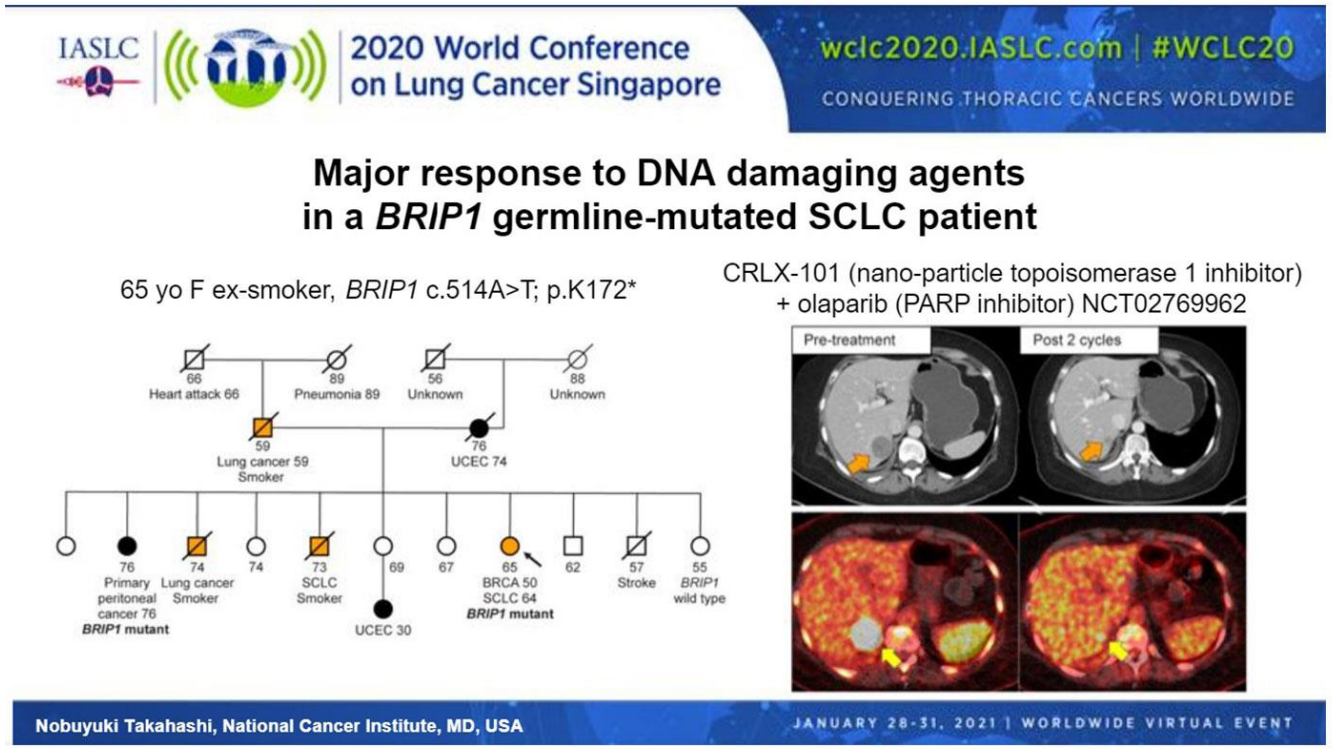
Studying 607 cancer predisposition genes

- **WES data from 77 pts with SCLC + 10 extrapulmonary** (+ additional cohort of 79 pts)

- **<u>43,7% of cases</u> with P/LP germline variants** (35 genes)

- **<u>10% - targeted therapy</u>**

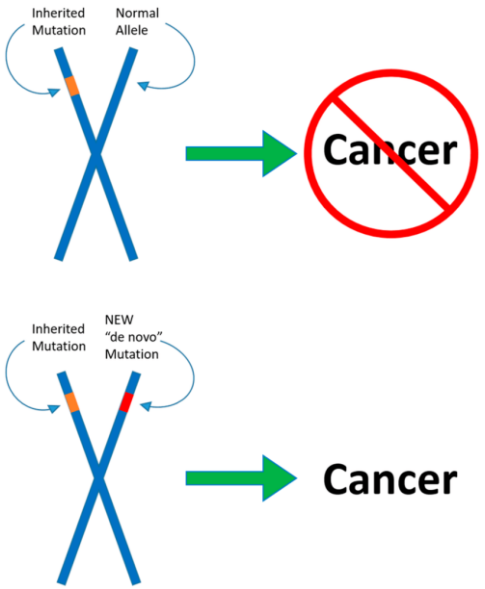
- **Correlation with outcomes**
  - PFS_ Platinum (HR 0.44)
  - Not with OS

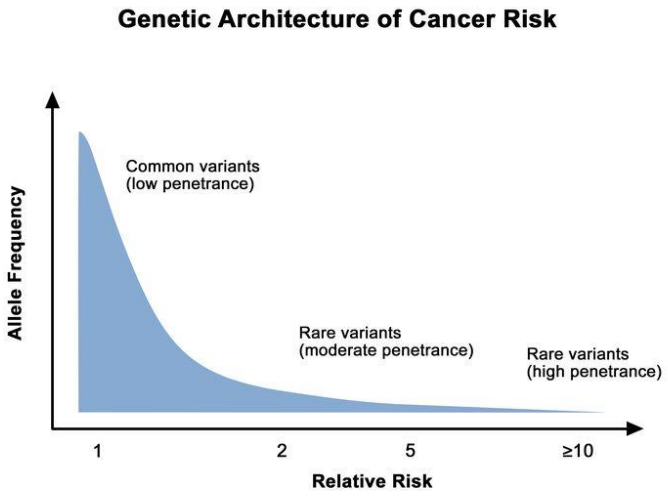


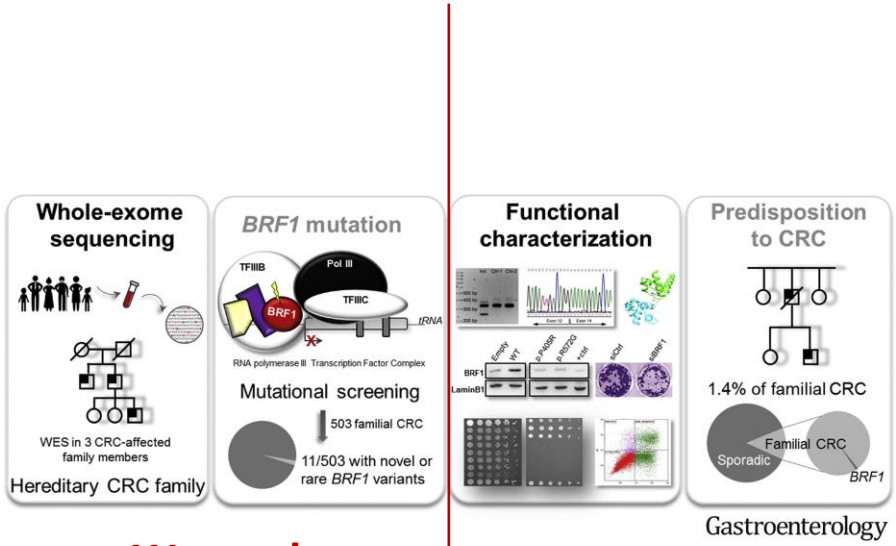
Takahashi et al, WCLC 2020

Challenge n#2: Data interpretation

Association ≠ Causality







We are here in lung cancer

https://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdq

Bellido F et al, Gastroenterology 2018

Robertson JC, et al, Cancers 2021

Challenge n#3: Data integration

INTRINSIC FACTORS

EXPOSURE TO CARCINOGENS

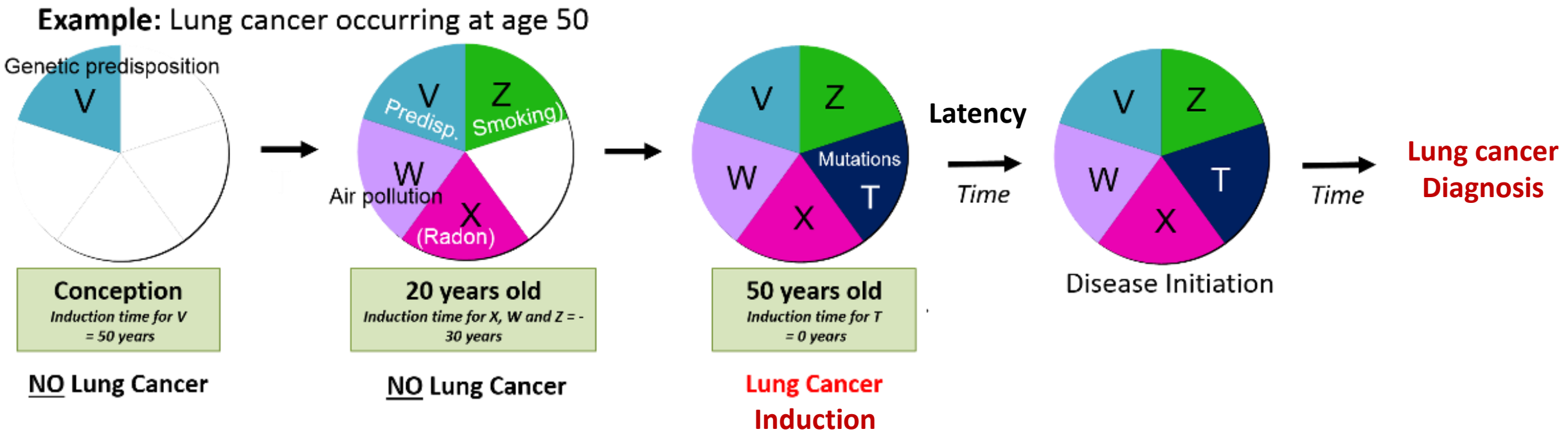
- **Nicotine & cyto P450**
- **DNA adducts**
- **DNA repair systems**
- **Hormonal differences**
- **Genetic differences**

- **Smoking**
- **Radon**
- **Other factors**
- **Life-style**
- **Occupations**

Barrera-Rodríguez & Morales-Fuentes, Lung cancer 2012

Challenge n#3: Data integration

Lung Cancer Exposome



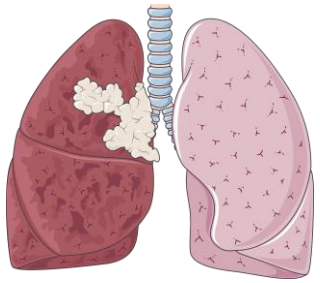
https://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH717-QuantCore/PH717-Module1A-Populations/PH717-Module1A-Populations8.html#headingtaglink_2

Near future: Think about what happened before (!)

Is this relevant for oncologists?

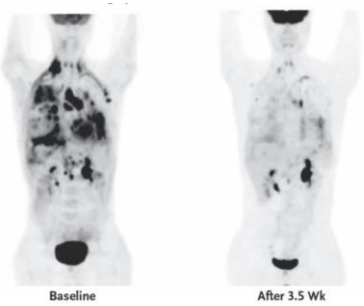
PATHOGENIC GERMLINE alt IMPACTS ON CANCER EVOLUTION

TYPE OF TUMOR



TREATMENT

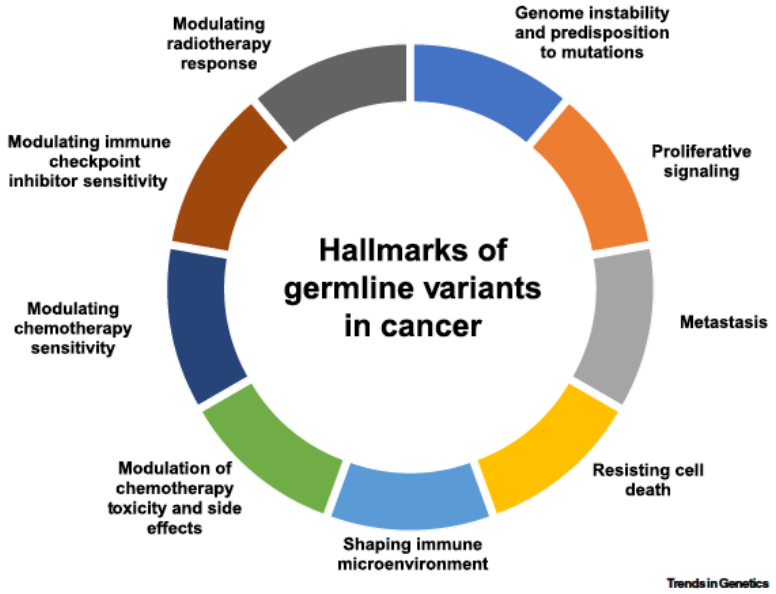
EVOLUTION



Oncologist

Near Future: Clinical impact in Lung cancer

TREATMENT = patient



Therapeutic approach
Prognosis

PREVENTION = family

Cascade studies

Chatrath, et al, Trends in Genetics, 2020

OUTLINE

- Familial & Genetic susceptibility in Lung Cancer
- Cancer predisposition in Lung Cancer
- Sex perspective
- ICAPEM research, challenges & future
- **Take home messages**

TAKE HOME MESSAGES

✓ **LUNG CANCER is a complex disease:**
- ≈ 2.3- 47% of NSCLC are PGVs-carriers

✓ **Profile of patients with NSCLC with PGV is <u>not well defined</u>**
- Sex related differences
- Slightly higher % in female pop, but not exclusively

✓ **We still need to identify the high-risk population in NSCLC**
- Patients & tumor profile: Female (?)
- Genes to study & data interpretation

✓ **Several challenges:** ICAPEM research projects ongoing

✓ **Germline alt. may potentially change the strategy for lung cancer**

GRACIAS!

Special THANKS to:

- **Dr. Juan Carlos Laguna**
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- Dr. Nuria Viñolas
- Dr. Roxana Reyes
- Dr. Noemi Reguart
- Dr. Marta Gª de Herreros
- Dr. Teresa Gorría
- Prof. Aleix Prat
- Dr. Montse Muñoz

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