VIII SIMPOSIUM
ICAPEM
Madrid, **7** de **noviembre** de 2024
PRESENCIAL
RETRANSMITIDO EN DIRECTO

Estudio INHERITY LC

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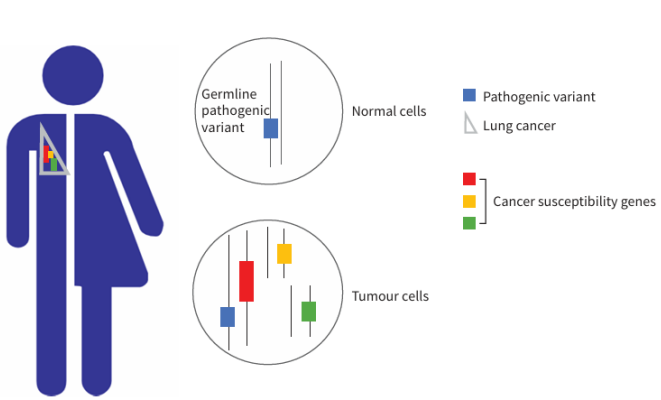
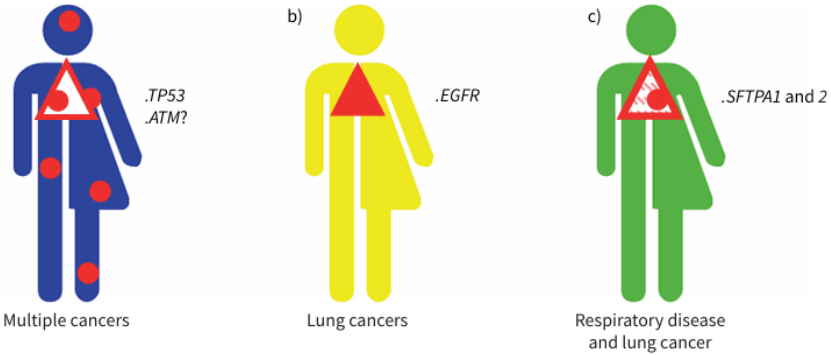
H.U La Paz

Lung cancer is also a hereditary disease

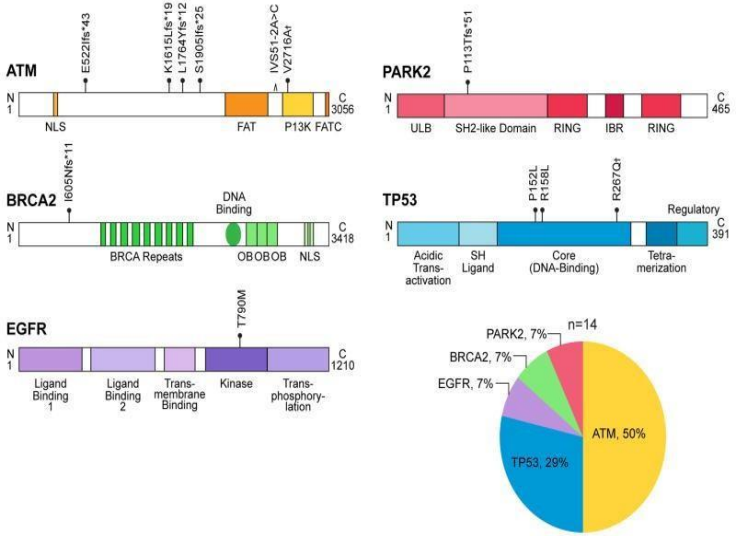




Prevalence of pathogenic germline variants (PGVs) in NSCLC between 2.3% and 14.9%

Peng W. Nat Commun 2022. Mukherjee S et al. Cancer Epidemiol Bio Prev. 2022.Mezquita et al. JTO 2023. Sorscher S et al. JCO 2023.

Lung cancer is also a hereditary disease



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

Prevalence of PGVs according to the Molecular group

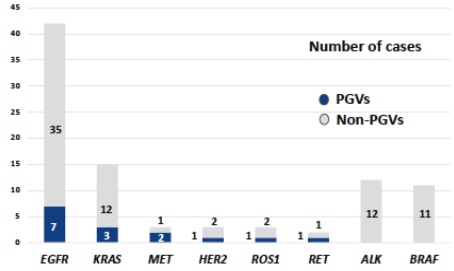


Figure 4. Frequency (N) of PGVs in each molecular group

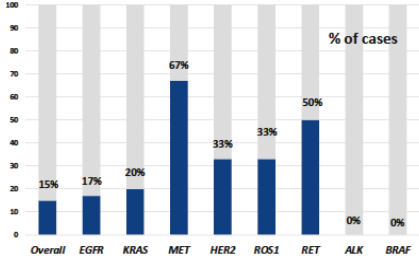


Figure 5. Frequency (%) of PGVs in each molecular group

Most common predisposition genes: ATM (50%), TP53, BRCA2, EGFR, PARK2

PGVs are probably associated with a <u>specific PROFILE</u> in lung cancer

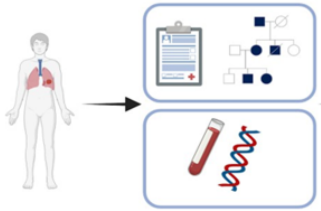
Mezquita L, et al, AACR 2021

INHERITY LC

- A prospective multicenter study aiming to investigate the prevalence of germline mutations in a selected cohort of patients with NSCLC.
- **INCLUSION CRITERIA**

1. **Family history** of NSCLC: one first-degree relative, or two or more second-degree relatives with NSCLC regardless of age
2. **Age and negative or low tobacco exposure**: diagnosis ≤ 45 years or ≤ 60 years with a pack-years ≤ 15
3. **Somatic actionable mutations** in tumor biopsy.

Material y Methods



N: 145
May 2021 to April 2023

NGS using a 72-gene customized panel

NextSeq™ System (Ilumina)

Bioinformatics analyses: *SOPHiA DDM™* Software

ACD	AIP	AKT1	APC	ATM
AXIN2	BAP1	BARD1	BMPR1A	BRCA1
BRCA2	BRIP1	CDH1	CDK4	CDKN2A
CHEK2	CTNNA1	DICER1	EPCAM	FH
FLCN	GREM1	HABP2	HOXB13	KIF1B
MAX	MC1R	MEN1	MET	MITF
MLH1	MLH3	MRE11	MSH2	MSH3
MSH6	MUTYH	NBN	NF1	NF2
NTHL1	PALB2	PIK3CA	PMS2	POLE
POT1	PRKAR1A	PRSS1	PTCH1	PTEN
RAD50	RAD51C	RAD51D	RB1	RET
SDHA	SDHAF2	SDHC	SDHD	SLC45A2
SMAD4	SMARCB1	STK11	SUFU	TERF2IP
TERT	TMEM127	TP53	VHL	XRCC2
SDHB	TOE1			

Pathogenicity : the American College of Medical Genetics and Genomics and the Association for Molecular Pathology consensus

Pathogenic variants (PV) and likely pathogenic variants (LPV)

Zurera ESMO 2024

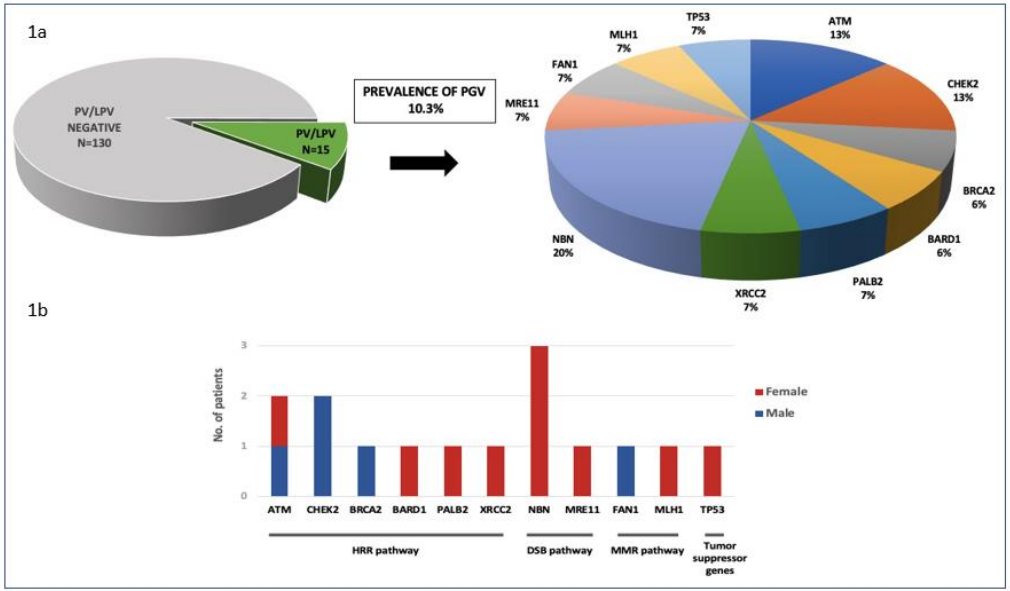
Material y Methods

Baseline characteristics of the study population and tumor characteristics.

Characteristics	Total population N=145
Median age at diagnosis [IQR range]	59 [48;68]
≤45 years	31 (21.4%)
46-60 years	50 (34.5%)
>60 years	64 (44.1%)
Sex	
Male	62 (42.8%)
Female	83 (57.2%)
Ethnicity	
Caucasian	135 (93.1%)
Asian	3 (2.07%)
Latin	7 (4.83%)
Smoking status	
Non-smoker	54 (37.2%)
Smoker (current/former)	91 (62.7%)
Median pack-years [IQR range]	12 [0;30]
≤15 pack-years	81 (55.9%)
16-40 pack-years	40 (27.6%)
>40 pack-years	24 (16.6%)
Synchronous or metachronous tumors	15 (10.3%)
Familiar history of cancer	
1st degree relatives with LC	51 (35.2%)
2nd /3rd degree relatives with LC	41 (28.3%)
1st degree relatives with other tumors	81 (55.9%)
2nd /3rd degree relatives with others t.	87 (60.0%)

Characteristics	Total population N=145
Histological type	
Adenocarcinoma	127 (87.6%)
Squamous cell carcinoma	12 (8.3%)
Large cell carcinoma	2 (1.4%)
NOS	4 (2.8%)
Disease stage	
Localized/Stage I-II	21 (14.5%)
Locally advanced/Stage-III	28 (19.3%)
Metastatic/Stage IV	96 (66.2%)
PD-L1 status	
<1%	54 (37.2%)
1-50%	34 (23.4%)
>50%	38 (26.2%)
Somatic mutations	
EGFR	48 (33.1%)
ALK	22 (15.2%)
ROS-1	6 (4.1%)
MET	4 (2.8%)
HER2	2 (1.4%)
KRAS	15 (10.3%)

Results



- 15 carriers harboring PGVs with a **prevalence of 10.3%**
- Most of the genes were involved in the DNA damage repair pathway (DDR)

Gen	cDNA change	Protein change	Variant	Age	Sex	Histology	Pack-years	Family history	Somatic mutation
XRCC2	c.190C>T	p.Arg64X	LPV	49	W	ADC	5	No	-
NBN	c.1648_1651delAAAA	p.Lys550fsX	LPV	53	W	ADC	0	Yes	-
FAN 1	c.326T>G	p.Leu109X	LPV	39	M	SCC	35	No	-
BRCA2	c.2701del	p.Ala902fs	PV	68	M	SCC	40	Yes	-
MRE11	c.820_821delCT	p.Leu274fs	PV	74	W	ADC	0	No	EGFR
CHEK2	c.1100delC	p.Thr367fs	PV	64	M	ADC	22	No	EGFR
MLH1	c.1459C>T	p.Arg487X	PV	58	W	ADC	0	No	EGFR
NBN	c.2140C>T	p.Arg714X	PV	50	W	ADC	25	No	ALK
ATM	c.901G>A	p.Gly301Ser	LPV	73	W	SCC	40	Yes	-
PALB2	c.1240C>T	p.Arg414Ter	PV	75	W	ADC	0	No	EGFR
CHEK2	c.499G>A	p.Gly167Arg	LPV	52	M	ADC	33	Yes	-
BARD1	c.157del	p.Cys53VAlfs*5	PV	66	W	ADC	7	No	HER2
ATM	c.8268+1G>C	p.?	LPV	63	M	NOS	20	No	KRASG12C
NBN	c.2071-2A>G	p.?	LVP	58	W	ADC	8,5	Yes	KRASG12C
TP53	c.476C>T	p.Ala159Val	PV	27	W	ADC	0	No	EGFR

***Table**: PV/LPV and clinicopathological characteristics; ADC: adenocarcinoma; SCC: squamous cell carcinoma; NOS: not otherwise specified.*

***Figure 1. 1a.** Prevalence of PGVs and frequency distribution according to mutation type. **1b**. Distribution of PGV by gender and molecular pathway classification. HRR: homologous recombination; DSB:double-strand break; MMR: mismatch repair.*

Results

Baseline characteristics of the study population and carriers PGVs

Characteristics	Total population N=145	PV/LPV N=15
Median age at diagnosis [IQR range]	59 [48;68]	58 [51;67]
≤45 years	31 (21.4%)	2 (13.3%)
46-60 years	50 (34.5%)	6 (40.0%)
>60 years	64 (44.1%)	7 (46.7%)
Sex		
Male	62 (42.8%)	5 (33.3%)
Female	83 (57.2%)	10 (66.7%)
Ethnicity		
Caucasian	135 (93.1%)	15 (100.0%)
Asian	3 (2.07%)	0 (0.0%)
Latin	7 (4.83%)	0 (0.0%)
Smoking status		
Non-smoker	54 (37.2%)	5 (33.3%)
Smoker (current/former)	91 (62.7%)	10 (66.7%)
Median pack-years [IQR range]	12 [0;30]	9 [0;29]
≤15 pack-years	81 (55.9%)	8 (53.3%)
16-40 pack-years	40 (27.6%)	7 (46.7%)
>40 pack-years	24 (16.6%)	0 (0.0%)
Synchronous or metachronous tumors	15 (10.3%)	2 (13.3%)
Familiar history of cancer		
1st degree relatives with LC	51 (35.2%)	5 (33.3%)
2nd /3rd degree relatives with LC	41 (28.3%)	2 (13.3%)
1st degree relatives with other tumors	81 (55.9%)	11 (73.3%)
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Characteristics	Total population N=145	PV/LPV N=15
Histological type		
Adenocarcinoma	127 (87.6%)	11 (73.3%)
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KRAS	15 (10.3%)	2 (13.3%)

Results

High selection criteria

Selection criteria	N (%)
Familiar history of lung cancer ▪ One first-degree relative with NSCLC or ▪ Two or more second-degree relatives with NSCLC	56 (38.6%)
Age and tobacco exposure ▪ Diagnose of NSCLC ≤ 45 years or ▪ Diagnose of NSCLC ≤ 60 years with a pack-years index ≤ 15	61 (42.0%)
Presence of somatic actionable mutations	102 (70.3%)
Number of criteria fulfilled	N (%)
1	80 (55.2%)
2	56 (38.6%)
3	9 (6.2%)

- A PGVs prevalence of 10.7% was found in pts with a known family history of LC.
- In pts **all three selection criteria**, a prevalence of PGVs of **22.2%** was found.

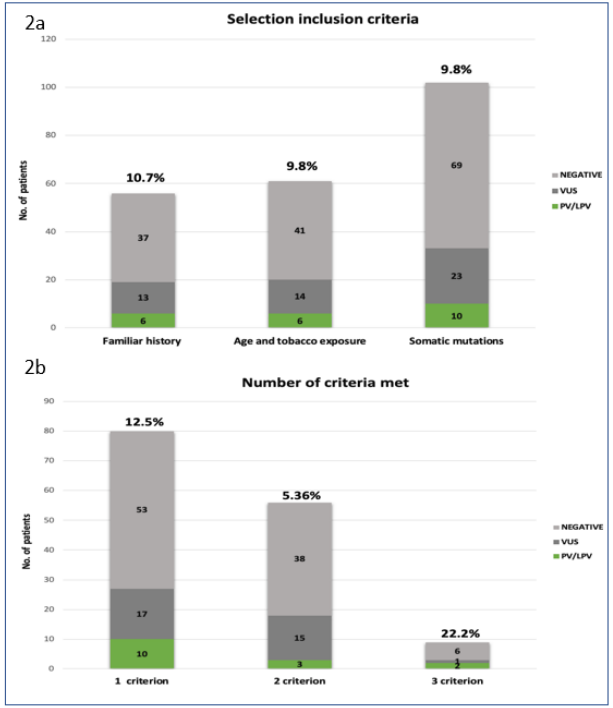


Figure2. 2a. *PGVs prevalence according to selection inclusion criteria.* ***2b.*** *PGVs prevalence according to number of criteria met.*

Results

Genetic Counseling Units (GCU) and patient impact

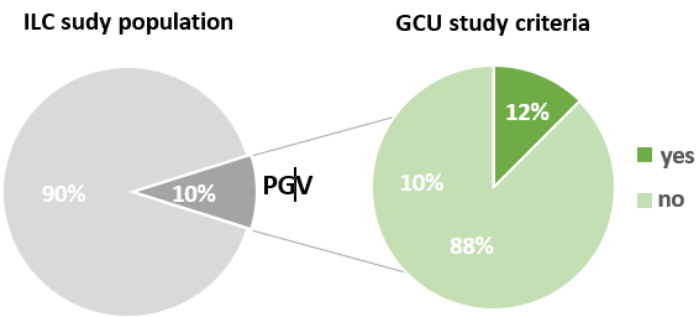


Figure 4. Proportion of patients with PGV with GCU study criteria.

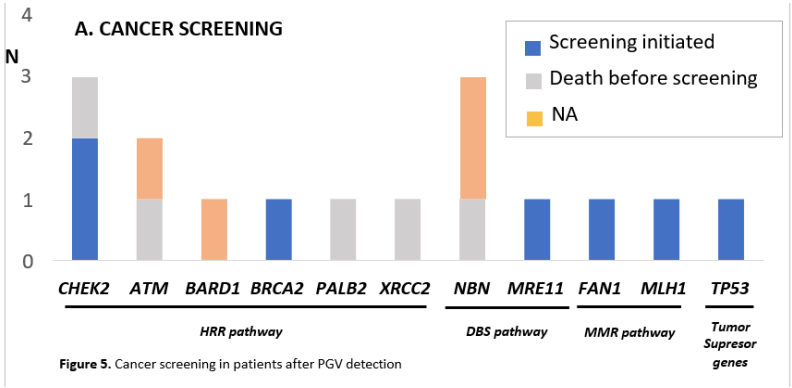


Figure 5. Cancer screening in patients after PGV detection

14 patients (88%) didn't met criteria for study in a GCU

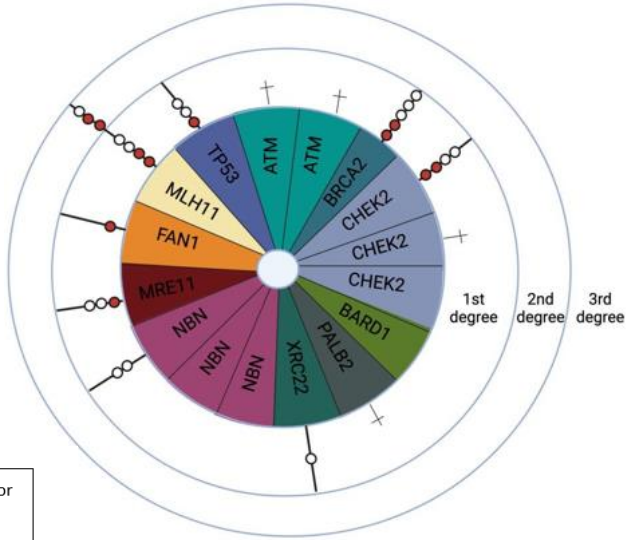
After detecting the PGV in the ILC, **all the patients were derived to a GCU**

In **7 patients (44%)** cancer screening for solid tumors has been initiated

In one patient with an *EGFR* mutated lung adenocarcinoma harboring a PGV in MLH1, a prophylactic hysterectomy was performed

Results

Genetic Counseling Units (GCU) and family impact



- In **10 families (63%) cascade study was commended** performing germline testing in 27 healthy relatives.
- Of them, in **12 individuals** a PGV was detected

Figure Cascade study in PGV-carriers. Relatives studied are represented by degree relationship

Inherity LC: Conclusions

- **The INHERITY LC study found a PGVs prevalence of 10% (22,2% among patients meeting all three selection criteria), with most of the genes involved in the DDR pathway.**
- **Data support previous findings of a possible implication of genetic predisposition as a risk factor for NSCLC**
- In this real-world cohort, **most of the carriers identified did not met criteria for genetic testing** according to the current guidelines.
- The discovery of PGVs in NSCLC led to **assessment and follow-up by GCU for both patients and their relatives** for cancer screening.
- **Germline testing and genetic counseling in NSCLC may have implications for prevention, early detection, and treatment.**
- ***TO BE CONTINUED…***

GRACIAS!

ICAPEM

Special THANKS to:

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- **Dra Laura Mezquita**
- **Dra Dolores Isla**
- **Dr Javier de Castro**