Germline testing in non-small cell lung cancer: Real-world impact of the discovery of germline pathogenic variants (PGV) in the INHERITY LC study

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BACKGROUND

- Recent data establish that the **prevalence of pathogenic germline variants (PGV)** in cancer presdisposing genes among patients with lung cancer ranges between **4-15%**[1-4]
- The **INHERITY LC (ILC) study** found a **PGV** prevalence of **11%** (16/148), particularly in genes involved in **DNA repair,** in patients with non-small cell lung cancer (NSCLC) prospectively enrolled[5].
- In contrast to other solid tumors with established criteria for study at **Genetic Counseling Units (GCU),** patients with lung cancer do not have specific criteria for GCU study, and its impact is unknown.

OBJECTIVE:

We aim to report the real-world impact of the discovery of PGVs in patients with NSCLC and their families

METHODS

- The **ILC study** (ICAPEM) enrolled a total of 148 patients with NSCLC with any of selection criteria collected in **table 1**. This is an **Ancillary study** assessing a total of **16 patients with NSCLC harboring PGVs** in cancer predisposition genes detected by germline testing in the ILC study.
- Germline genetic testing was performed by **next-generation sequencing (NGS)** using a 61-gene panel (Hereditary Cancer Solution, Sophia Genetics).
- Demographic clinical data, personal/family history of cancer, as well as the clinical/molecular data of NSCLC were collected from medical records
- Assessment in a GCU was collected for PGV-carriers after germline testing. **Post-GCU study decisions**, including cancer screening, and risk reduction strategies in patients; cascade study and PGVs identified in their relatives, were analyzed.

1) familiar history of lung cancer: 1st-degree relative, or 2 or more 2nd-degree relatives with NSCLC regardless of age
2) age and negative or low tobacco exposure: diagnose ≤ 45 yo. or ≤ 60 yo. with PY ≤ 15
3) presence of somatic actionable mutations in the tumor biopsy

Table 1. Selection criteria of ILC study. PY: pack-year, yo: year-old

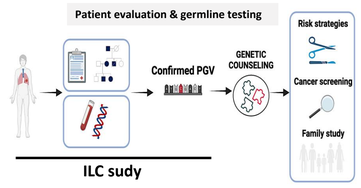


Figure 1. INHERITY LC (ILC) study design and impact of GCU study. Figure adapted from *Laguna et al, BJC 2024.*

RESULTS

Study population with PGV

Baseline characteristics (%)		
Age	Median, range	60 (31-79)
Gender	Male	6 (38)
	Female	10 (62)
Smoking status	Ever-smokers	11 (69)
	Non-smokers	5 (31)
Histology	Adenocarcinoma	11 (69)
	Squamous	4 (25)
	Others	1 (6)
Stage	Stage IV	11 (69)
	Non stage IV	5 (31)
PDL1 status	≤1%	5 (31)
	1-50%	4 (25)
	≥50%	6 (37)
	No data	1 (6)
Molecular status	Driver*	9 (56)
	No Driver	6 (27)
	Missing	1 (6)

Table 2. Baseline characteristics (N=16)

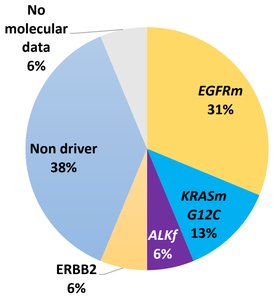


Figure 2. Distribution of the study population by molecular status.

*Driver population was defined as somatic mutations (m) in *EGFR/KRAS/BRAF/MET/ERBB2*, fusions (f) in *ALK/ROS1/RET/NTRK1-3* and amplifications (a) in *ERBB2/MET*)

GCU study & Patient Impact

GCU study

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

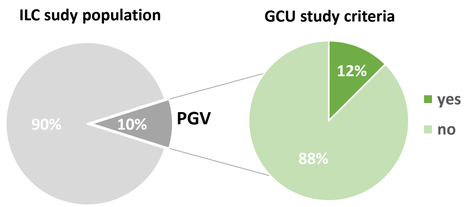


Figure 4. Proportion of patients with PGV with GCU study criteria.

- After detecting the PGV in the ILC, **all the patients were derived to a GCU** but 3 patients were not studied because of patient death

Cancer prevention measures in patients after GCU study

- In **7 patients (44%)** cancer screening for solid tumors has been initiated while in 6 (37%) was not initiated because of death for cancer progression

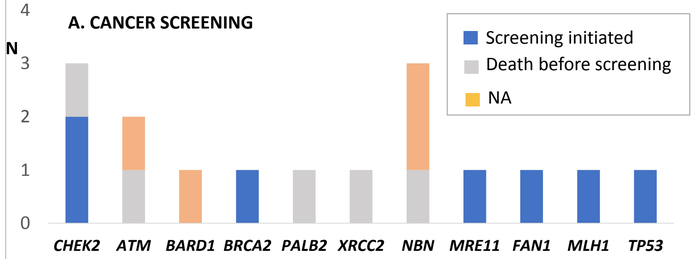
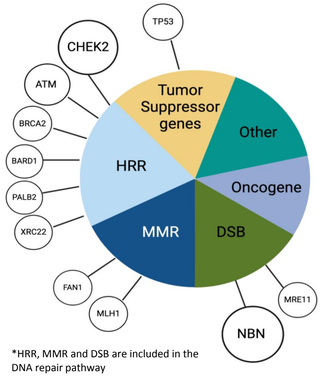


Figure 5. Cancer screening in patients after PGV detection

B. RISK REDUCTION

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

Genes & Pathways altered in PGV-carriers



*HRR, MMR and DSB are included in the DNA repair pathway

The PGV detected affected genes mainly related with **DNA repair**, followed by Tumor Suppressor genes

DNA repair genes:
- HRR: 56%
- DSB: 25%
- MMR: 13%

Tumor Suppresor Genes: 6%

Figure 3. Distribution of PGV in cancer predisposition genes by pathway. Circle size depend on the number of PGV detected. DSB: Double-Strand breaks repair, HRR: Homologous Recombination, MMR: Mismatch Repair.

Family impact

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

Figure 6. Cascade study in PGV-carriers. Relatives studied are represented by degree relationship.

CONCLUSIONS

- 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.
- Specific criteria for genetic testing in patients with NSCLC are needed

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DISCLOSURES: JCL has no disclosures to declare