Original Study

Germline Mutation Analysis and Real-World Impact in a Selected Cohort of Patients with Non-Small Cell Lung Cancer: INHERITY LC Study

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Abstract

The INHERITY LC study evaluated 145 selected NSCLC patients, identifying pathogenic germline variants in 10.3%, mainly in DNA damage repair genes. After one year of follow-up, cascade testing identified 12 healthy carriers. These findings support the potential relevance of germline testing and counseling in NSCLC for prevention, early detection, and management, warranting further validation.

Purpose: Hereditary predisposition has not traditionally been considered a significant risk factor for non-small-cell lung cancer (NSCLC), and germline testing is not routinely established. INHERITY LC is a prospective multicenter study designed to explore the prevalence of germline variants in a selected cohort of patients with NSCLC and to assess the clinical impact of germline testing in NSCLC. **Methods:** Germline genetic testing was conducted using next-generation sequencing (NGS) using a 72-gene panel. 145 patients with NSCLC who met one of the following criteria were selected: 1) family history of NSCLC; 2) young age and negative/low tobacco exposure; or 3) presence of somatic actionable mutations. **Results:** Pathogenic germline variants (PGVs) were identified in 15 patients (10.3%; 95% CI, 5.9-16.3), involving the following genes: BRCA2 (1), CHEK2 (2), ATM (2), PALB2 (1), BARD1 (1), XRCC2 (1), MRE11 (1), NBN (3), FAN1 (1), MLH1 (1), and TP53 (1). A notably higher prevalence of PGVs (22%) was observed among patients who met all three selection criteria. After 1 year of prospective follow-up, cascade testing was performed in PGV-positive families, leading to the identification of 12 healthy relatives carrying PGVs. **Conclusion:** The INHERITY LC study identified a PGV prevalence of 10.3% in a selected NSCLC cohort, with most variants affecting genes involved in the DNA damage repair (DDR) pathway. The application of specific selection criteria may enhance the yield of germline testing in this

Abbreviations: NSCLC, non-small cell lung cancer; PGV, pathogenic germline variants; NGS, next-generation sequencing; DDR, DNA damage repair; LC, lung cancer; LCINS, lung cancer in never-smokers; TKIs, tyrosine kinase inhibitors; PCR, polymerase chain reaction; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; PV, pathogenic variants; LPV, likely pathogenic variants; GCU, genetic counseling unit; IQR, interquartile range; HR, homologous recombination; DSB, double-strand break repair; MMR, mismatch repair; VUS, variants of uncertain significance; PARPi, poly ADP-ribose polymerase inhibitors.

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setting. Larger confirmatory studies are warranted to demonstrate that germline testing and genetic counseling for NSCLC may have implications for prevention, early detection, and treatment.

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Introduction

Lung cancer (LC) is the leading cause of cancer-related mortality worldwide in both men and women, with an incidence rate of 26.6 per 100.000 and accounting for 1.8 million deaths.[1] With an estimated 2.2 million new cases per year, LC is the second most commonly diagnosed cancer, representing 11.4% of all newly diagnosed malignancies.[2]

Tobacco exposure remains the primary risk factor for the development of LC.[3] However, approximately 10% to 20% of LCs are not attributable to smoking.[4] Other environmental risk factors unrelated to tobacco exposure include asbestos, arsenic, radon, polycyclic aromatic hydrocarbons, or household air pollution from solid fuels.[5,6] Lung cancer in never-smokers (LCINS) is most commonly diagnosed in women, at a younger age onset, and in individuals of East Asian origin, mainly NSCLC with adenocarcinoma subtype and often harbor oncogenic driver alterations.[7]

Emerging evidence suggests that genetic predisposition may contribute to the pathogenesis of LC, particularly in LCINS. Patients with a positive family history of a first-degree relative with LC have been shown to have a 50% increased risk of developing LC.[8] Several case reports of families with a high prevalence of LC and a mendelian inheritance pattern have described the presence of PGVs in *EGFR* (V834I, 2R776H, T790M, V834L),[9-12] *YAP1* (R331W)[13] or *PARK2*.[14] While the somatic T790M mutation is associated with acquired resistance to first and second-generation EGFR tyrosine kinase inhibitors (TKIs), germline T790M mutations have been described in treatment- naïve patients with familial-EGFR mutant NSCLC,[15] with an estimated lifetime risk of developing NSCLC of approximately 23%.[16] Li-Fraumeni syndrome caused by PGVs in the *TP53* gene, is an autosomal dominant disease predisposing individuals to develop different tumor types, including NSCLC, reported in 2% to 7% of cases.[17]

The introduction of NGS analysis has facilitated the widespread adoption of molecular testing in oncology and has expanded the understanding of the molecular and hereditary landscape of various cancers, including NSCLC. Unlike other tumors, hereditary predisposition has not traditionally been considered a relevant risk factor for LC, and germline genetic testing is not routinely performed. However, genetic testing may have important implications for risk assessment in patients carrying PGVs, by enabling tailored surveillance strategies aimed at reducing the risk of second primary malignancies and, in selected cases, informing therapeutic decisions. It also has implications for at-risk relatives, as it facilitates cascade testing, preventive interventions, and early cancer detection strategies.[18]

Preliminary studies estimate that the prevalence of PGVs in patients with NSCLC ranges from 2.3% to 14.9%, with a notable proportion involving genes associated with the DDR pathway.[19-25] INHERITY LC is a prospective multicenter study aiming to investigate the prevalence of germline mutations in a selected cohort of patients with NSCLC and to evaluate the impact of germline testing in NSCLC.

Material and Methods

Study Design and Patient Selection

The INHERITY LC study explores the presence of germline mutations in a cohort of 145 Spanish patients with a diagnosis of NSCLC that fulfill at least one of the following selection criteria: 1) Family history of NSCLC: 1 first-degree relative, or two or more second-degree relatives with NSCLC regardless of age; or 2) Age and negative or low tobacco exposure: diagnosis $\leq$ 45 years or $\leq$ 60 years with a pack-years $\leq$ 15; or 3) Presence of somatic actionable mutations in the tumor biopsy.

Actionable somatic mutations were defined as genomic alterations with targeted therapies currently available in routine clinical practice or under evaluation in clinical trials. The following genes were considered: EGFR, ALK, ROS1, KRAS, BRAF, ERBB2, MET (exon 14 skipping mutation), RET, and NTRK. Somatic testing was performed at each participating center according to locally approved diagnostic workflows and availability. Standardized methods included single-gene assays such as polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH), as well as multigene next-generation sequencing (NGS) approaches. Specifically, the Oncomine Focus Assay (Thermo Fisher Scientific) was used for NGS-based molecular profiling. The Idylla platform (Biocartis, Belgium) was employed for the rapid detection of mutations in the EGFR, KRAS, NRAS, and BRAF genes. For ALK rearrangements, FISH was performed using the ALK IQFISH Break-Apart probe (Agilent Technologies), and IHC analysis employed the Ventana ALK (D5F3) clone (Roche). ROS1 rearrangements were assessed by IHC using the ROS1 (D4D6) Rabbit mAb (Cell Signaling Technology). EGFR mutations were also analyzed using the Cobas 4800 EGFR Mutation Test (Roche Diagnostics).

All patients provided informed consent and the study was approved by the Institutional Review Board. Clinical data were obtained from institutional electronic medical records and patient interviews to gather family history and pedigrees. Blood samples for germline analysis were collected from May 2021 to April 2023 at 3 Thoracic Tumors Cancer Units in Spain. Germline genetic testing was centralized and performed by NGS using a 72-gene panel (Supplemental Table 1).

DNA extraction from blood lymphocytes was performed with magLEAD (Precision System Science Co.) The exonic and intronic

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regions with demonstrated clinical relevance of the genes described above have been studied using the NextSeq™ System by Illumina. Library preparation and enrichment have been made by Hereditary Cancer Solution, using a customized panel of 72 high/moderate-penetrance cancer susceptibility genes. The bioinformatics analyses were performed by SOPHiA DDM Software. 100% coverage of the genes analyzed is achieved, with a depth of 50x for 100% of the sequences analyzed and greater than 200x for 99.9% of the sequences analyzed.

The interpretation of results and identification of pathogenicity of germline variants were performed according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology consensus and recommendations.[26] Gene-specific guides were also used when available. We consider positive testing for PGV including pathogenic variants (PV) and likely pathogenic variants (LPV). Confirmation by Sanger sequencing was carried out.

Prospective follow-up was conducted for all the patients in whom a PGV was identified, 12 months after the germline testing, to evaluate the clinical impact of the genetic counseling unit (GCU) intervention in these patients. Post-GCU outcomes were documented, including the specific measures implemented for both patients and their relatives.

Statistical Analysis

Quantitative variables were described using the median and interquartile range (IQR), while qualitative variables were summarized as absolute numbers and percentages. Comparisons of quantitative variables among 3 groups were performed using the Kruskal–Wallis test, and pairwise comparisons between specific groups (patients without mutations vs. those with PGVs) were conducted using the Mann–Whitney U test. Associations between qualitative variables were evaluated using Fisher's exact test or the chi-square test with Yates correction, as appropriate. Proportions were reported with 95% confidence intervals (CIs) calculated using the Wilson method. A P-value $< .05$ was considered statistically significant.

Results

Patients Characteristics

A total of 145 participants were included in the study. Baseline characteristics of the total study population are summarized in (Table 1). Median age at diagnosis was 59 (IQR range, 48 to 68) with a prevalence of women (57.2%), and Caucasian ethnicity in 93.1%. Regarding the family history of cancer, 35.2% and 55.9% of patients had a first-degree relative with LC and other tumors respectively. The histological subtype was predominantly adenocarcinoma in 87.6% of patients. The disease stage was metastatic in 66.2% of the study population, whereas 19.3% had a locally advanced disease and 14.5% had localized disease at the time of enrolment. *EGFR* was the most frequent somatic mutation detected in 32.1% of patients, followed by *ALK* (14.5%), KRAS (9.6%), *ROS-1* (4.1%), *MET* (2.1%), *ERBB2* (1.4%), and *BRAF* (1.4%) (Supplemental Table 2).

The proportion of patients included by selection criteria and the number of criteria fulfilled are summarized in Table 2. The presence of somatic actionable mutation was the main selection criterion, with 95 patients included. 38.6% of the cohort fulfilled two selection criteria and 6.2% met all 3 criteria.

Germline Analysis

We found fifteen carriers harboring PGV including PV/LPV with a prevalence of 10.3% (15/145; 95% IC: 5.9-16.6) in this selected cohort of 145 patients. PGV and their correlation with clinicopathological characteristics are detailed in Table 3. Most of them were involved in the DDR genes: *CHEK2* ($n = 2$), *ATM* ($n = 2$), *BRCA2* ($n = 1$), *PALB2* ($n = 1$), *BARD1* ($n = 1$), *XRCC2* ($n = 1$) in the homologous recombination (HR) pathway; *MRE11*($n = 1$) and *NBN* ($n = 3$) involved in the double-strand break repair (DSB) pathway; *FAN1* ($n = 1$) and *MLH1* ($n = 1$) in DNA mismatch repair (MMR) pathway. Followed by tumor suppressor genes: *TP53* ($n = 1$) (Figure 1A). Patient carriers of PGV were predominantly female (67%) (Figure 1B), adenocarcinoma histological subtype (73%) (Figure 1B), and with negative or low tobacco exposure with a median of 9 pack-years (IQR range, 0 to 29) (Table 1). 42 variants of uncertain significance (VUS) were found in 36 patients (Supplemental Table 3).

Analysis by Selection Inclusion Criteria

A prevalence of 10.7% (6/56; 95% CI, 5.0-21.1) of carriers with PV/LPV was found among patients with a known family history of LC, according to the selection criteria (Figure 2). A prevalence of 9.8% (6/61; 95% CI, 4.6-19.8) was observed among patients selected by age and tobacco exposure, and a prevalence of 9.8% (10/102; 95% CI, 5.4-17.0) was observed among those identified due to the presence of a somatic mutation. When focusing on the number of criteria fulfilled, the PGV prevalence was 22.2% (2/9; 95% CI, 6.3-54.7) in patients meeting all 3 selection criteria, however, no linear increase was found between the number of PGVs detected and the number of criteria fulfilled ($P = .373$).

Genetic Counseling Assessment and Real-World Impact

An observational prospective follow-up of all PV/LPV carriers was performed 12 months after germline genetic testing. 93% of the PGV carriers ($n = 14/15$) identified in the INHERITY LC study did not meet the criteria for genetic testing and GCU assessment according to the current recommendations.[27-30] 13 patients were referred to a GCU, while 2 patients could not be referred due to cancer-related death at the time of receiving the genetic test results. Figure 3A shows the flowchart of patient assessment in a GCU after PGV detection.

Cancer screening was indicated after genetic counseling in 7 patients (54%), including colorectal and endometrial cancer screening for patients harboring PGV in MMR genes; and breast and ovarian cancer or prostate cancer screening for female and male patients, respectively, harboring PGV in HR genes. Despite the GCU study, in 6 patients (46%), cancer screening was not indicated due to the absence of clinical benefit in the context of advanced LC or death. Risk-reducing hysterectomy was indicated after the detection of a PV in *MLH1* in a female patient with a stage III lung adenocarcinoma after LC-specific treatment.

A family cascade study was conducted in 10 families (67%), testing 27 healthy relatives. Figure 3B represents family cascade

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Figure 1 Results of PGV analysis in 145 patients. A. Prevalence of PGV and frequency distribution according to mutation type. B. Distribution of PGV by sex (left) and histology (right). The molecular pathway classification of each gene is shown above the bar graph.

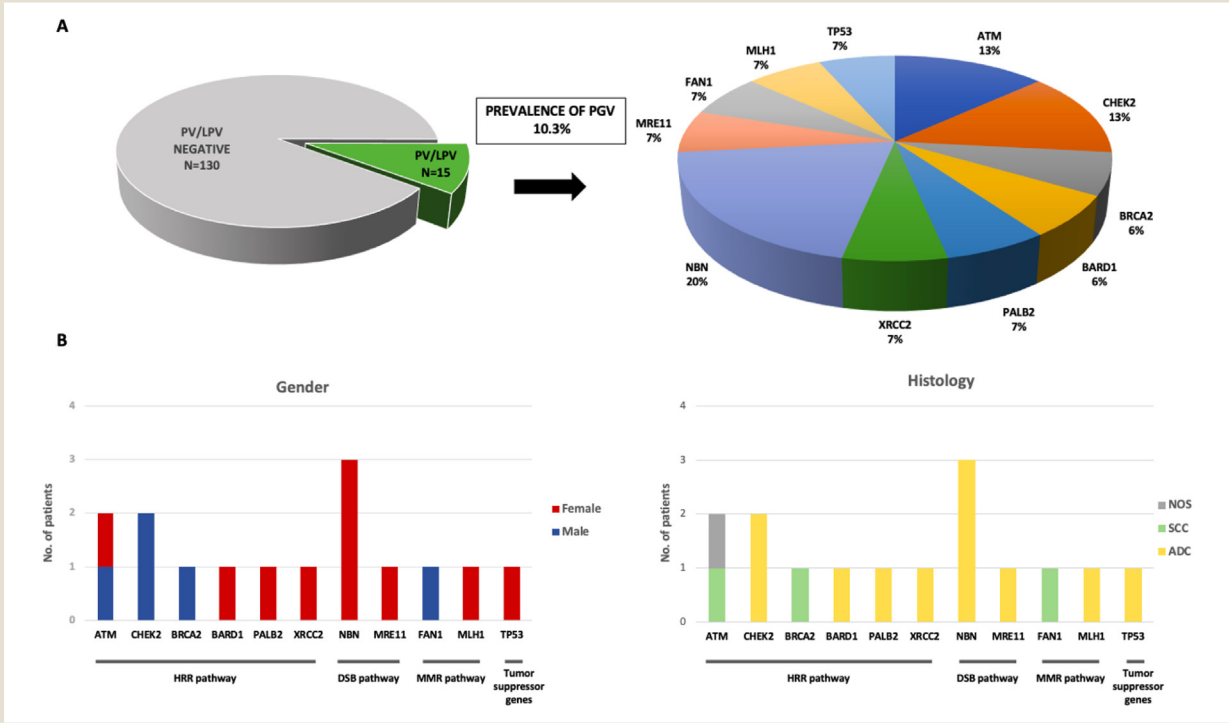

Figure 2 PGV prevalence according to selection inclusion criteria. The numbers inside the bar chart represent the total number of patients meeting each criterion, distributed by color according to the analysis result: negative, VUS, or PV/LPV.

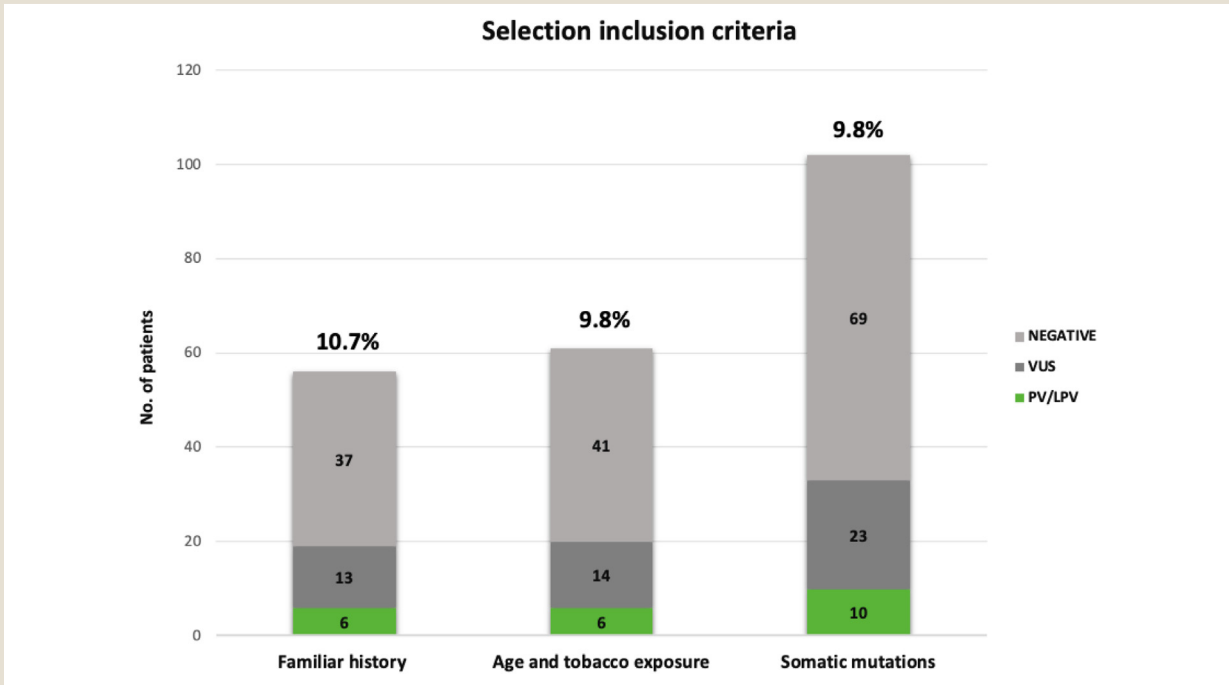

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Table 1 Baseline Characteristics of the Study Population and Histologic Subtypes

Characteristics	Total Population $n = 145$	PV/LPV $n = 15$	Non-PV/LPV $= 130$	*P* Value
Median age at diagnosis [IQR range]	59 [48;68]	58 [51;67]	59.0 [48;68]	.99
≤ 45 years	31 (21.4%)	2 (13.3%)	29 (22.3%)	
46-60 years	50 (34.5%)	6 (40.0%)	44 (33.8%)	
> 60 years	64 (44.1%)	7 (46.7%)	57 (43.9%)	
Sex				.90
Male	62 (42.8%)	5 (33.3%)	57 (43.8%)	
Female	83 (57.2%)	10 (66.7%)	73 (56.2%)	
Ethnicity				1.00
Caucasian	135 (93.1%)	15 (100.0%)	120 (92.3%)	
Asian	3 (2.07%)	0 (0.0%)	3 (2.3%)	
Latin	7 (4.83%)	0 (0.0%)	7 (5.4%)	
Smoking status				
Non-smoker	54 (37.2%)	5 (33.3%)	49 (37.7%)	
Smoker (current/former)	91 (62.7%)	10 (66.7%)	81 (62.3%)	
Median pack-years [IQR range]	12 [0;30]	9 [0;29]	12.5 [0;30]	.90
≤ 15 pack-years	81 (55.9%)	8 (53.3%)	73 (56.1%)	
16-40 pack-years	40 (27.6%)	7 (46.7%)	33 (25.4%)	
> 40 pack-years	24 (16.6%)	0 (0.0%)	24 (18.5%)	
Synchronous or metachronous tumors	15 (10.3%)	2 (13.3%)	13 (10.0%)	.65
Familiar history of cancer				1.00
First degree relatives with LC	51 (35.2%)	5 (33.3%)	46 (35.4%)	
Second /Third degree relatives with LC	41 (28.3%)	2 (13.3%)	39 (30.0%)	
First degree relatives with other tumors	81 (55.9%)	11 (73.3%)	70 (53.8%)	
Second /Third degree relatives with other tumors	87 (60.0%)	10 (66.7%)	77 (59.2%)	
Histological type				.15
Adenocarcinoma	127 (87.6%)	11 (73.3%)	116 (89.2%)	
Squamous cell carcinoma	12 (8.3%)	3 (20.0%)	9 (6.9%)	
Large cell carcinoma	2 (1.4%)	0 (0.0%)	2 (1.5%)	
NOS	4 (2.8%)	1 (6.7%)	3 (2.31%)	
Disease stage				1.00
Localized/stage I-II	21 (14.5%)	2 (13.3%)	19 (14.6%)	
Locally advanced/stage-III	28 (19.3%)	3 (20.0%)	25 (19.2%)	
Metastatic/stage IV	96 (66.2%)	10 (66.7%)	86 (66.2%)	
PD-L1 status				.59
< 1%	54 (37.2%)	5 (33.3%)	49 (43.8%)	
1%-50%	34 (23.4%)	3 (20.0%)	31 (27.7%)	
> 50%	38 (26.2%)	6 (40.0%)	32 (28.6%)	
Somatic mutations				1.00
EGFR	48 (33.1%)	5 (33.3%)	43 (35.2%)	
ALK	22 (15.2%)	1 (6.7%)	21 (17.2%)	
ROS-1	6 (4.1%)	0 (0.0%)	6 (4.92%)	
MET	4 (2.8%)	0 (0.0%)	4 (3.1%)	
HER2	2 (1.4%)	1 (6.7%)	1 (0.8%)	
KRAS	15 (10.3%)	2 (13.3%)	13 (10.0%)	

Abbreviations: IQR = interquartile range; LC = lung cancer; NOS = not otherwise specified; PV/LPV = pathogenic variants/likely pathogenic variants.

testing by PGV of the index case. Overall, 12 healthy individuals were PGV carriers of the same germline alteration identified in the study. Specifically, PGV in *BRCA2, CHEK2, FAN1, MLH1, MRE11, NBN, TP53,* and *XRCC2* were detected. Currently, all individuals are under follow-up by GCU for preventive measures. No data is available about specific results of cancer screening/preventive measures for relatives at 12 months of follow-up.

To determine the therapeutic implications of PGV, we classified all 15 PV/LP variants identified using the OncoKB classification system according to the level of evidence for the gene as a predic-

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Figure 3 Preventive impact of PGV detection in patients with LC. A: Flowchart of evaluation and preventive measures implemented in patients with LC after the PGV detection. B: A representation of cascade testing over healthy relatives by PGV detected. Each circle represents a relative: white circles for relatives tested and negative germline test, red if they harbor the same PGV as the patient with LC. Crosses represent patient deaths before the GCU study or measure implementation.

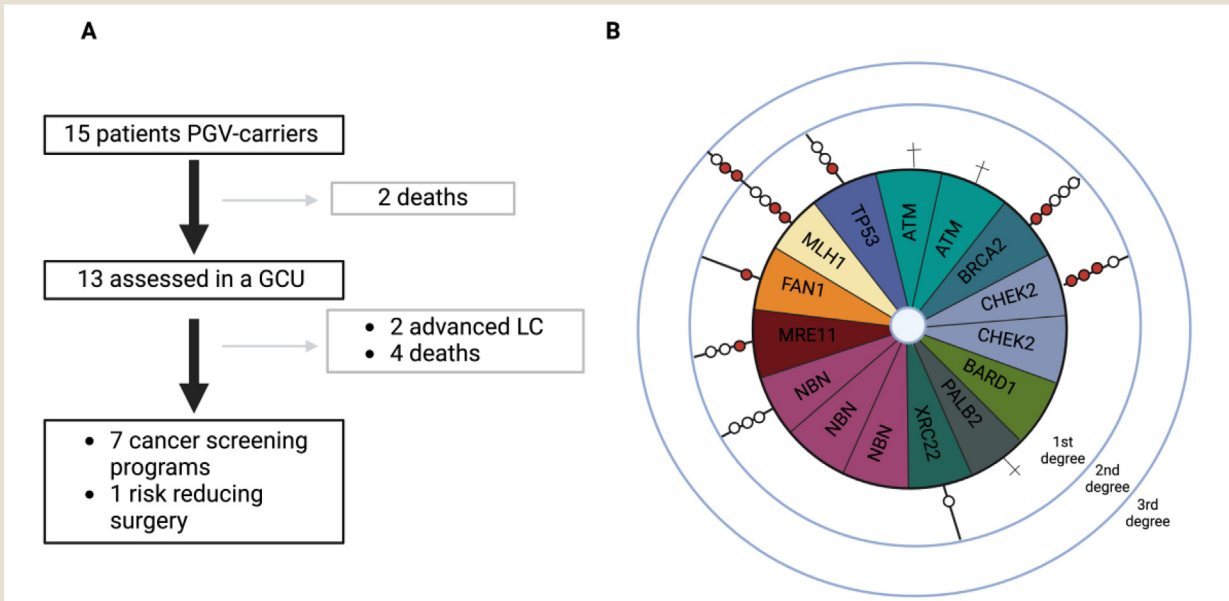

Table 2 Proportion of Patients Included by Selection Criteria and Number of Criteria Fulfilled

Selection Criteria	n (%)
Familiar history of lung cancer	56 (38.6%)
• One first-degree relative with NSCLC or	
• Two or more second-degree relatives with NSCLC	
Age and tobacco exposure	61 (42.0%)
• Diagnose of NSCLC ≤ 45 years or	
• Diagnose of NSCLC ≤ 60 years with a pack-years index ≤ 15	
Presence of somatic actionable mutations	95 (65.5%)
Number of criteria fulfilled	N (%)
1	80 (55.2%)
2	56 (38.6%)
3	9 (6.2%)

Abbreviation: NSCLC = non-small cell lung cancer.

tor of drug sensitivity.[31] Overall, 80% of patients (n = 12/15) harbored a PGV in a potentially therapeutically actionable gene (*ATM, BARD1, BRCA2, CHEK2, MLH1, MRE11, NBN, PALB2*). All of them were classified as level 3B due to their role as predictive biomarkers in other solid tumors.

Discussion

We report findings from a prospective selected cohort of 145 NSCLC patients, revealing a prevalence of PGVs of 10.3%. This prevalence appears higher than that reported in the general population, estimated at approximately 1% to 2% for established cancer predisposition genes such as BRCA1, BRCA2, CHEK2, and ATM in large population-based studies.[32,33] Notably, lung cancer has not been specifically represented in these population-based analyses. Large-scale sequencing studies in unselected cohorts of patients with cancer have described germline mutation rates ranging from 5% to 10% across tumor types.[30,34] In addition, retrospective studies of patients with lung cancer have reported PGV frequencies between 2.3% and 14.9%.[19-25] The reported prevalence varies considerably across studies, reflecting differences in populations and methodologies, which limit the possibility of direct comparisons.

When assessing the clinical utility of germline testing, pretest probability is a key consideration in determining when genetic evaluation becomes justified. In other tumor types, such as breast, ovarian, or colorectal cancer, predictive models such as BOADICEA/CanRisk or PREMM5[35,36] support germline testing when the probability of carrying a pathogenic variant exceeds approximately 5% to 10%. In our study, the 10.3% prevalence observed suggest that germline evaluation may also be clinically relevant in selected NSCLC populations. Nevertheless, further studies with larger sample sizes and appropriate control groups are warranted to confirm these findings.

In our cohort, PGVs were more frequently observed among patients with adenocarcinoma subtype, females, and those with negative or low tobacco exposure. The majority of PGVs identified were in genes involved in the DDR pathway, including *BRCA2, CHEK2, ATM, PALB2*, and *NBN*. This finding aligns with previ-

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Table 3 P/LP Variants and Clinicopathological Characteristics

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	ERBB2
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

Abbreviations: ADC = adenocarcinoma; LPV = likely pathogenic variant; NOS = not otherwise specified; PV = pathogenic variants; SCC = squamous cell carcinoma.

ously published cohorts where a high proportion of DDR genes were reported.[18,20-24] However, these findings do not indicate causality. Biallelic inactivation has been investigated in previous studies to elucidate a potential connection between these germline mutations and lung carcinogenesis. A study of 1794 Chinese lung cancer patients reported a prevalence of PGV of 5.91%, with evidence of second-hit genes with PGV/LPGV in tumor biopsy of 18.6%.[21] Another series[23] observed biallelic inactivation in 75% of lung adenocarcinoma patients carrying PGV in tumor suppressor genes (*TP53, BAP1, MEN1*) and in more than 40% of carriers of 4 DDR genes (*ATM, BRCA2, CHEK2, MRE11*). Interaction with tobacco exposure and other risk factors for LC remains unclear and warrants further investigation, including functional studies.

Although *KRAS G12C* mutations are classically linked with tobacco exposure, we included them in our analysis because emerging evidence suggest that germline variants, particularly in DNA repair genes, may modulate the somatic mutational profile of NSCLC, increasing the likelihood or the relative frequency of actionable driver mutations such as *KRAS* G12C. For instance, a study in patients with germline *CHEK2* mutations reported that more than 40% harbored actionable somatic drivers, with *KRAS* G12C being the most frequent.[37] Similarly, in a Chinese cohort, patients with PGVs were significantly enriched for somatic *MET* alterations, mainly exon 14 skipping mutations, as well as *KRAS* mutations.[21] In our study, we identified 2 patients with *KRAS* G12C who also harbored PGVs in *ATM* and *NBN*, highlighting the need for larger studies to validate these findings.

Unlike in other solid tumors, there are no well-established recommendations for germline genetic testing in LC. Current guidelines restrict germline testing in LC primarily to *EGFR* T790M mutations prior to TKI treatment; and *TP53* and *STK11* in patients with specific clinical phenotypes.[30] The absence of broader criteria that account for age, smoking history or tumor molecular features may result in missed opportunities for PGVs detection and, consequently, exclusion from GCU evaluation. Notably, in our study, most of the PGV carriers (93%) did not meet current guideline-based criteria for germline testing.[27-30]

Interestingly, PGV identification in patients with LC led to referral to the GCU in all cases, providing access to evaluation for both patients and their relatives. Advanced LC or death were the main reasons for no recommendation of preventive measures in our cohort. Nevertheless, cancer screening for other solid tumors was recommended in more than half of the patients studied, especially in patients with early stage LC. Given the aggressive nature of LC, with approximately half of new cases diagnosed at advanced stages,[38] early implementation of genetic risk evaluation is crucial to maximize the impact of germline testing in thoracic oncology. Cascade testing, defined as the systematic identification and evaluation of at-risk relatives following the detection of a PGV in a proband, constitutes a central objective in hereditary cancer care. In our study, 27 healthy relatives underwent genetic evaluation following the identification of a patient harboring a PGV, who might otherwise have remained underdiagnosed.

Beyond the role of genetics in preventive measures, certain actionable PGV can grant access to specific treatments in certain solid tumors. For instance, PGVs in HR genes such as *BRCA1/BRCA2* could be targeted with PARP inhibitors (PARPi). To date, few studies have evaluated the efficacy of PARPi in combination with other therapeutic modalities in NSCLC. Overall, no clear benefit of adding PARPi has been reported in NSCLC, although most studies did not perform patient selection by germline data or HR deficiency phenotype.[39-41] Post-hoc analysis in some studies have found that *BRCA* mRNA levels could act as a predictive biomarker of PARPi in patients with EGFR-mutant tumors.[42] Another potential actionable PGV found in our cohort was *MLH1, as* MMR genes have been associated with a particular microsatellite instability tumor phenotype with a particular sensibility to immune-checkpoint inhibition in colorectal and other solid tumors.[43,44]

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Despite the prospective design of our study, which included detailed family history documentation and pedigree analysis, the relatively small sample size represents a key limitation and warrants cautious interpretation of the findings. In addition to this constraint, several challenges must be considered when extrapolating these results to real-world clinical practice. Barriers such as the accessibility and cost of germline testing, the frequent diagnosis of NSCLC at advanced stages—which limits the implementation of preventive interventions—and the need for specialized genetic counseling may restrict widespread application. Although lung cancer screening programs based on low-dose computed tomography have been shown to reduce mortality in high-risk populations,[45,46] their implementation remains limited and not yet generalized across healthcare systems. Moreover, no evidence is currently available regarding the potential impact of applying such strategies specifically to individuals carrying germline pathogenic variants, representing an unmet need for future research. Additional challenges include the interpretation of variants of uncertain significance (VUS), which often creates uncertainty for both clinicians and patients, complicating decision-making and counseling. Furthermore, disclosure of germline results may cause psychological distress or anxiety among patients and their relatives. These factors highlight the need for careful pre-test counseling, ethical consideration, and structured follow-up when integrating germline testing into thoracic oncology practice.

Conclusion

The INHERITY LC study is a prospective, multicenter study with specific selection criteria for germline testing in patients diagnosed with NSCLC. The study identified a PGV prevalence of 10.3%, with most of the genes involved in the DDR pathway. After 1 year of prospective follow-up, a meaningful clinical impact was observed through the identification of 12 healthy individuals with PGVs, who are currently under preventive follow-up at a GCU. Our data support previous findings of a possible implication of genetic predisposition as a risk factor for LC, although these data remain hypothesis-generating. Larger confirmatory studies are warranted to demonstrate that germline testing and genetic counseling for NSCLC may have implications for prevention, early detection, and treatment.

Clinical Practice Points

There is currently no robust evidence or consensus in clinical guidelines supporting routine germline testing in patients with lung cancer, except in specific circumstances (eg, the presence of an *EGFR* T790M mutation in patients without prior exposure to tyrosine kinase inhibitors, or suspected Li-Fraumeni syndrome). However, germline testing may be appropriate in selected patients with non-small-cell lung cancer (NSCLC) when clinical suspicion is warranted. Genetic counseling and cascade testing for individuals carrying pathogenic germline variants may have significant implications for cancer prevention and early detection in both patients and their at-risk relatives.

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Disclosure

The authors declare no potential conflicts of interest or disclaimers related to the content of this study.

CRediT authorship contribution statement

María Zurera: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. **Juan Carlos Laguna:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Laura Mezquita:** Writing – review & editing, Methodology, Conceptualization. **Oliver Higuera:** Writing – review & editing, Methodology, Conceptualization. **Sebastián Menao:** Writing – review & editing, Methodology, Investigation. **María Arruebo:** Methodology, Investigation, Writing – review & editing. **Javier Torres Jimenez:** Methodology, Writing – review & editing. **Javier de Castro:** Writing – review & editing, Methodology, Conceptualization. **Dolores Isla:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Rodrigo Lastra:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization.

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Supplementary Material

Supplementary Table 1 Next Generation Sequence Panel of 72 high/moderate-penetrance cancer susceptibility genes.

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			

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Supplementary Table 2 Somatic mutation profile, germline analysis results and clinical characteristics.

Pt.	Somatic mutation	PGV	LPGV	VUS	Age	Sex	Pack-years	Family history
2	EGFR	-	-	-	60	W	0	No
10	EGFR	-	-	-	38	W	0	No
12	EGFR	-	-	-	68	W	0	Yes
24	EGFR	-	-	ATM	47	W	0	No
25	EGFR	-	-	-	68	W	0	No
29	EGFR	-	-	CDH1	61	W	0	No
38	EGFR	-	-	-	70	M	0	No
42	EGFR	-	-	-	81	M	20	No
43	EGFR	-	-	ATM	60	W	0	No
46	EGFR	-	-	-	71	W	0	No
47	EGFR	-	-	-	59	M	15	No
48	EGFR	-	-	-	54	M	22,5	No
49	EGFR	MRE11	-	-	74	W	0	No
51	EGFR	-	-	ATM	75	M	15	No
52	EGFR	-	-	-	70	W	0	No
53	EGFR	-	-	ATM	72	M	60	No
58	EGFR	-	-	APC	58	M	12	No
60	EGFR	-	-	-	66	W	0	No
62	EGFR	-	-	BAP1	87	M	70	Yes
63	EGFR	CHEK2	-	BRF1	64	M	22	No
66	EGFR	-	-	-	43	W	0	No
67	EGFR	-	-	-	44	W	0	No
69	EGFR	-	-	-	76	M	6	No
70	EGFR	MLH1	-	PALB2	58	W	0	Yes
72	EGFR	-	-	BRIP1	56	W	0	No
73	EGFR	-	-	-	48	W	10	No
75	EGFR	-	-	BRCA2, NF1	60	W	0	Yes
81	EGFR	PALB2	-	-	75	W	0	No
83	EGFR	-	-	BRCA1	56	W	35	No
85	EGFR	-	-	-	59	W	2,5	No
87	EGFR	-	-	-	62	W	46	No
88	EGFR	-	-	MRE11	70	W	0	No
91	EGFR	-	-	-	58	W	0	Yes
93	EGFR	-	-	-	87	M	0	No
104	EGFR	-	-	-	64	W	29	No
109	EGFR	-	-	-	33	W	2	Yes
111	EGFR	-	-	-	36	M	2	No
120	EGFR	-	-	-	70	M	55	No
122	EGFR	-	-	MRE11, POLE	56	M	8	No
132	EGFR	-	-	-	54	M	0	No
133	EGFR	-	-	-	61	W	0	No
135	EGFR	-	-	-	54	W	0	Yes
137	EGFR	-	-	-	44	W	0	No
140	EGFR	-	-	-	76	W	10	No
149	EGFR	-	-	-	61	M	0	No
151	EGFR	TP53	-	-	27	W	0	No
152	EGFR	-	-	TP53	53	W	25	No
4	ALK	-	-	-	67	W	0	No
19	ALK	-	-	BRCA2	72	W	20	No

(*continued on next page*)

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Supplementary Table 2 (*continued*)

Pt.	Somatic mutation	PGV	LPGV	VUS	Age	Sex	Pack-years	Family history
21	ALK	-	-	-	66	W	0	No
22	ALK	-	-	BRIP1	39	M	5	No
23	ALK	-	-	-	37	W	0	No
27	ALK	-	-	-	69	M	0	No
33	ALK	-	-	-	41	W	0	No
37	ALK	-	-	-	47	M	0	No
41	ALK	-	-	-	51	M	14	No
44	ALK	-	-	-	80	W	0	Yes
50	ALK	-	-	KIT	55	W	0	No
76	ALK	-	-	-	56	M	10	No
79	ALK	NBN	-	-	50	W	25	No
90	ALK	-	-	-	45	W	0	No
100	ALK	-	-	-	58	M	30	No
113	ALK	-	-	-	45	W	0	No
117	ALK	-	-	-	63	W	0	No
123	ALK	-	-	-	80	W	0	No
126	ALK	-	-	-	48	M	0	No
127	ALK	-	-	ATM	51	W	10	No
144	ALK	-	-	-	51	M	30	No
145	ALK	-	-	-	69	W	0	No
14	ROS1	-	-	-	52	W	18	No
18	ROS1	-	-	-	59	W	0	Yes
110	ROS1	-	-	-	39	M	5	No
139	ROS1	-	-	-	42	W	0	No
141	ROS1	-	-	-	41	W	0	No
150	ROS1	-	-	-	24	W	0	No
36	KRAS	-	-	BRCA2, PDGFRA	63	W	20	No
98	KRAS	ATM	-	-	63	M	20	No
107	KRAS	-	-	-	63	M	45	Yes
112	KRAS	-	-	-	68	W	0	No
115	KRAS	NBN	-	-	58	W	8,5	Yes
77	KRAS	-	-	APC	75	M	30	Yes
78	KRAS	-	-	SDHAF2	75	W	42	Yes
89	KRAS	-	-	-	72	M	54	No
92	KRAS	-	-	-	76	M	80	No
103	KRAS	-	-	-	60	M	30	Yes
106	KRAS	-	-	-	74	M	60	Yes
114	KRAS	-	-	-	60	W	19	No
118	KRAS	-	-	-	58	W	67	Yes
121	KRAS	-	-	-	44	M	40	No
153	KRAS	-	-	-	76	M	15	Yes
97	ERBB2	BARD1	-	-	66	W	7	No
96	ERBB2	-	-	-	52	W	15	No
71	MET	-	-	-	86	W	0	Yes
105	MET	-	-	FLCN	60	M	30	No
108	MET	-	-	-	61	W	5	No
94	BRAF	-	-	-	48	W	15	Yes
147	BRAF	-	-	-	43	W	15	Yes

Pt: Patient; W: women; M:male LPV: likely pathogenic variant; PV: pathogenic variants; VUS: variant of uncertain significance.

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Supplementary Table 3 Variants of unknown significance and clinical and clinicopathological characteristics

Pt.	Gen	cDNA change	Protein change	Age	Sex	Histology	Pack-years	Family history	Somatic mutation
24	ATM	c.2012T>A	p.Ile671Lys	47	W	ADC	0	No	EGFR
28	ATM	c.7618G>A	p.Val2540Ile	66	M	ADC	40	Yes	-
43	ATM	c.6820G>A	p.Ala2274Thr	60	W	ADC	0	No	EGFR
51	ATM	c.610G>A	p.Gly204Arg	75	W	ADC	15	No	EGFR
53	ATM	c.6101G>A	p.Arg2034Gln	72	M	ADC	60	No	EGFR
65	ATM	c.4724G>A	p.Arg1575His	67	M	ADC	61	Yes	-
65	ATM	c.6820G>A	p.Ala2274Thr	67	M	ADC	61	Yes	-
68	ATM	c.680C>T	p.Ser227Leu	44	W	ADC	10	No	-
127	ATM	c.2167G>A	p.Val723Met	51	W	ADC	10	Yes	ALK
58	APC	c.4016G>A	p.Gly1339Asp	58	M	ADC	12	No	EGFR
58	APC	c.3773C>A	p.Thr1258Lys	58	M	ADC	12	No	EGFR
77	APC	c.7378G>C	p.Ala2460Pro	75	M	NOS	30	Yes	KRAS
62	BAP1	c.1058T>C	p.Ile353Thr	87	M	ADC	70	Yes	EGFR
55	BRCA1	c.2655C>A	p.Phe885Leu	39	M	SCC	35	No	-
83	BRCA1	Ex24dupl	GRCH37:CHR17:41196270-41197938	56	W	ADC	35	No	-
3	BRCA2	c.6137C>T	p.Ser2046Leu	72	W	ADC	20	No	ALK
36	BRCA2	c.1564G>C	p.Gly522Arg	63	W	ADC	20	No	KRAS
57	BRCA2	c.6937+4A>G		67	M	SCC	70	Yes	-
75	BRCA2	c.5660C>T	p.Thr188Met	60	W	ADC	0	Yes	EGFR
19	BRF1	c.79G>A	p.Ala27Thr	64	M	ADC	80	Yes	-
63	BRF1	c.272G>A	p.Arg91His	64	M	ADC	22	No	EGFR
22	BRIP1	c.1941G>T	p.Trp647Cys	39	M	ADC	5	No	ALK
57	BRIP1	c.1735C>T	p.Arg579Cys	67	M	SCC	70	Yes	
72	BRIP1	c.2285G>A	p.Arg762His	56	W	ADC	0	No	EGFR
29	CDH1	c.1930G>A	p.Asp644Asn	61	W	ADC	0	No	EGFR
105	FLCN	c.445G>A	p.Gly149Ser	60	M	ADC	30	No	MET
64	FH	c.1433_1434insAAA	p.Lys477dup	54	W	ADC	30	Yes	-
50	KIT	c.1487A>T	p.Asp496Val	55	W	ADC	0	No	ALK
54	MLH1	c.1690C>T	p.Leu564Phe	60	W	ADC	8	Yes	-
28	MRE11	c.476T>C	p.Val159Ala	66	M	ADC	40	Yes	-
88	MRE11	c.1029G>C	p.Met343Ile	70	W	ADC	0	No	EGFR
122	MRE11	c.1207G>A	p.Glu403Lys	56	M	ADC	3	No	EGFR
35	MSH2	c.13C>G	p.Pro5Ala	65	M	SCC	50	Yes	-
99	MSH2	c.1631T>A	p.Ile544Asp	74	M	SCC	70	No	KIT
75	NF1	c.6971 A>G	p.Gln2324Arg	60	W	ADC	0	Yes	EGFR
70	PALB2	c.3433G>A	p.Gly1145Ser	58	W	ADC	0	No	EGFR
116	PALB2	c.664_666del	p.Leu222del	59	W	ADC	0	Yes	-
36	PDGFRA	c.3218del	p.Met1073fs	63	W	ADC	20	No	KRAS
3	POLD1	c.1320 G>T	p.Gln440His	64	M	ADC	80	Yes	-
34	POLE	c.2251A>G	p.Asn751Asp	44	W	LCC	40	Yes	-
122	POLE	c.5174T>C	p.Val1725Ala	56	M	ADC	3	No	EGFR
154	POLE	c.4100A>G	p.Tyr1367Cys	44	W	ADC	0	No	EGFR
78	SDHAF2	c.44G>A	P.Glu150Lys	75	W	ADC	42	Yes	KRAS
152	TP53	c.167A>G	p.Glu56Gly	53	W	ADC	25	No	EGFR

Pt: Patient; W: women; M:male; ADC: adenocarcinoma; SCC: squamous cell carcinoma; NOS: not otherwise specified; LCC: large cell carcinom

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