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Family history enrichment in Non-Small cell Lung Cancer: A cross-sectional – prospective study to inform referral for germline testing

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ABSTRACT

Background: Family history of cancer (FHC) is a recognized proxy of inherited cancer susceptibility. In NSCLC, however, the clinical relevance of FHC remains poorly defined, and standardized approaches to identify patients enriched for pathogenic germline variants (PGVs) are lacking.

Methods: FAHIC-Lung (NCT06196424) is a multicenter, cross-sectional/prospective observational study conducted in Italy. Consecutive patients with NSCLC were enrolled, detailed FHC data were collected using a dedicated questionnaire covering cancer type, age at diagnosis, degree of relatedness, smoking exposure, and other risk factors among relatives. A weighted FHC score integrating cancer burden across first-, second-, and third-degree relatives and accounting for family structure and degree of genetic relatedness was developed. Percentile-based thresholds (≥90th percentile, or ≥ 75th percentile with additional risk factors) were used to identify patients with enriched familial cancer profiles.

Results: Among 336 evaluable patients, median age at diagnosis was 67 years, 49.7% were female, and 25.9% were never smokers. Cancer in at least one parent was reported in 63.1% of cases, while 27.7% of patients had a personal history of multiple primary malignancies. The median total FHC score was 0.40 (interquartile range 0.12–0.67). Thirty-three patients (9.5%) exceeded the 90th percentile threshold, and 22 patients (6.5%) met the 75th percentile threshold in association with clinical enrichment criteria. Overall, 55 patients (16.4%) were identified as having enriched familial cancer risk and were selected as a target population for systematic genetic counseling and planned germline testing.

Conclusions: In this prospective observational study, a standardized and weighted assessment of family history identified a clinically meaningful subset of patients with NSCLC enriched for familial cancer patterns. This framework provides a pragmatic approach to optimize referral to genetic counseling and supports targeted

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germline screening strategies beyond traditional smoking-based risk models. Prospective validation in the planned translational phase will clarify the clinical utility of this approach.

1. Introduction

Family history of cancer is a recognized proxy of inherited cancer susceptibility and plays a central role in clinical management of several malignancies, including breast, ovarian, colorectal, and prostate cancer [1–3]. In these settings, specific familial patterns such as early age at diagnosis, recurrence of related tumor types, and the occurrence of multiple primary malignancies within families are considered clinically relevant indicators of potential germline predisposition [1–3].

In non-small cell lung cancer (NSCLC), by contrast, the clinical significance of family history of cancer remains less clearly defined [4]. Despite lung cancer being one of the leading causes of cancer related mortality worldwide [5], available evidence addressing familial cancer patterns in this population is limited and highly heterogeneous [4]. Published studies report widely variable rates of family history of cancer, reflecting differences in study design, definitions of family history, degree of relatedness considered, and the frequent lack of detailed information on tumor type, age at diagnosis, and shared environmental or behavioral risk factors among relatives. [4] Most data derive from retrospective analyses relying on simplified definitions of family history, which may fail to capture clinically meaningful familial signals [4].

From a clinical and public health perspective, this gap has important implications. In the absence of standardized, prospectively collected data, the identification of patients with NSCLC who may be enriched for pathogenic germline variants (PGVs) remains largely empirical, limiting both the effectiveness and the sustainability of germline screening strategies. A structured characterization of family history of cancer (FHC) is therefore needed to identify, in a statistically powered and clinically validated manner, target populations most likely to benefit from genetic counseling and germline testing. Such an approach may allow the detection of familial clustering effects suggestive of inherited predisposition, optimize the allocation of genetic counseling resources, and even support the implementation of screening strategies beyond traditional risk profiles dominated by tobacco exposure.

In this context, the FAHIC Lung study (NCT06196424) was designed as a prospective observational study to provide a standardized and comprehensive assessment of family history of cancer and within-family clusters of other risk factors in patients with NSCLC to identify patients to be systematically referred for genetic counseling and PGVs / likely PGVs screening. In the present analysis, we report the results of the observational phase of the study, focusing on the prevalence and composition of familial cancer history in an unselected cohort of patients with NSCLC.

2. Methods

Study Design and objectives.

The FAHIC-Lung study is a cross-sectional, prospective, observational, multicenter study designed to investigate the family history of cancer (FHC) in patients with NSCLC (ClinicalTrials.gov identifier: NCT06196424). The overarching objective was to identify FHC patterns and within-family clusters of risk factors in order to guide patients toward systematic genetic counseling and germline next-generation sequencing (NGS) testing to detect PGVs and likely PGVs.

The study was conceived as a two-phase project, with the observational phase designed to be completed first, to inform power calculations

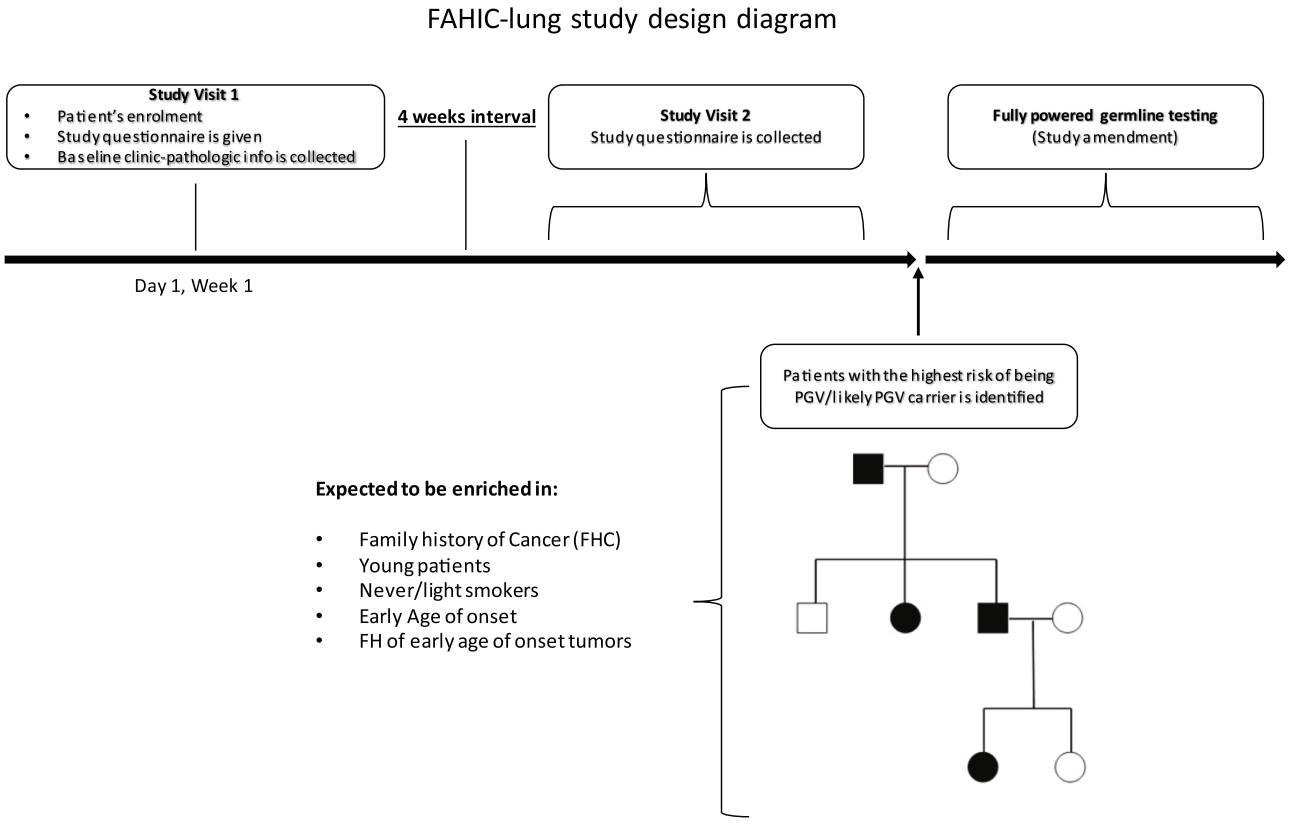

Fig. 1. Schematic representation of the FAHIC-Lung study design. Abbreviations: FHC, family history of cancer; NSCLC, non-small cell lung cancer; PGV, pathogenic germline variant; NGS, next-generation sequencing. *Adapted from Citarella et al., Journal of Translational Medicine, 2024.*

and fixed selection criteria for the subsequent translational phase, which will be implemented following a predefined protocol amendment (Fig. 1).

Consecutive patients with histologically confirmed NSCLC were enrolled at participating sites in Italy, regardless of age, TNM stage, smoking status, or other clinicopathologic characteristics. Inclusion criteria included: histopathological diagnosis of NSCLC (all stages); age $\geq$ 18 years; signed written informed consent; availability of familial and/or personal anamnestic data of cancer. Exclusion criteria included: unavailability of familial and/or personal cancer history; patient refusal for any cause.

For the purpose of the study, relatives were classified by degree of relatedness according to standard genetic and biomedical definitions, as commonly adopted in clinical genetics and familial cancer risk assessment.

- First-degree relatives: parents, full siblings, and offspring (expected to share approximately 50% of germline genetic material);
- Second-degree relatives: uncles and aunts only (approximately 25% shared genetic material);
- Third-degree relatives: first cousins, defined as offspring of uncles and aunts (approximately 12.5% shared genetic material).

The expected proportion of shared genetic material refers to average germline inheritance under Mendelian segregation and is used here as a conceptual framework rather than an exact individual-level estimate.

We limited the inclusion of second-degree relatives to uncles and aunts and of third-degree relatives to first cousins, based on concerns related to recall bias, increased missingness, and reduced reliability of data on more distant relatives such as grandparents or great-uncles.

Patients' family history was meticulously collected using a dedicated, self-reported study questionnaire specifically developed in Italian for the FAHIC study and validated by a clinical geneticist on the steering committee (available as **supplementary material**). The questionnaire and the composite FHC score represent a novel tool specifically developed for the FAHIC-Lung study and have not been previously used or externally tested. The involvement of a clinical geneticist in the steering committee provided conceptual and content appraisal to ensure clinical plausibility and consistency with established principles of familial cancer risk assessment.

The questionnaire captured detailed information on:

- Family history of cancer;
- Tumor types and primary sites in affected relatives;
- Age at diagnosis of affected relatives;
- Sex of affected relatives;
- Smoking status and exposure in affected relatives;
- Geographical origin of the participant and relatives;
- Personal history of multiple malignancies;
- Potential environmental or occupational exposure to carcinogens in the patient and family;
- Ethnicity of the patient and relatives.

To minimize recall bias, all patients were followed up over two study visits within four weeks. At the initial visit, clinicopathologic data were collected, and participants received the questionnaire, which was returned at the follow-up visit.

Collected clinical and pathological data included: smoking status (active/passive, pack-years, smoking duration); smoking status by pack-years (light smokers were defined as patients below the 10th percentile of the pack-year distribution in the study population); age at NSCLC diagnosis; tumor histology; TNM stage (8th edition); ethnicity; environmental/occupational exposure; known oncogenic drivers (focusing on EGFR point mutations and ALK gene translocation); history of other malignancies (defined has having a positive history of synchronous or metachronous additional malignant tumor); passive smoking exposure (defined as having at least 1 parent who smoked). Passive smoking exposure in the index patient was defined as parental smoking behavior and was used as a pragmatic proxy of early-life household exposure. Other sources of passive smoking exposure (e.g., spousal or household exposure in adulthood) were not systematically assessed.

Family trees were reconstructed for each participant, incorporating segregation of environmental exposures, smoking history, and other risk factors to detect familial clustering potentially linked to germline PGVs or likely PGVs.

All patients with missing data (even partially) on any category of relatives were conservatively assigned a value of zero for the corresponding component of the FHC score. However, the extent of missing data was systematically recorded and reported, allowing transparent assessment of potential recall limitations, even though missingness was not modeled explicitly in the score computation.

Importantly, to mitigate the differential expression of familial risk based on the number of relatives (e.g., a participant who is an only child has an unexpressed risk of family history that cannot be classified the same as another participant with N° siblings, none of whom have a history of cancer), we developed a ratio that accounted for the presence or absence of different types of relatives by introducing a weighting system.

In addition, to quantitatively assess the burden of familial cancer history, we developed a structured FHC score. The composite FHC score integrates cancer burden across first-, second-, and third-degree relatives using a weighted framework that accounts for degree of genetic relatedness and family structure. The score was designed as a pragmatic tool to capture gradients of familial cancer aggregation, rather than a binary family history variable, with full methodological details provided in the **Supplementary Methods**.

Non-family-related risk factors considered included early NSCLC onset ($\leq$50 years), multiple malignancies, never/light smoking, oncogene addiction (EGFR/ALK), absence of passive smoking, and lack of occupational/environmental carcinogen exposure.

- Patients with a total weighted FHC score $\geq$ the 90th percentile were classified as high-priority candidates for germline sequencing.
- Those with a score $\geq$ the 75th percentile and either early-onset NSCLC, multiple primary malignancies, or at least being never/light smokers and two additional of the aforementioned non-familial risk factors were also included.

The distribution of the FHC score was explored descriptively, and predefined percentile thresholds were used to identify enriched familial profiles. The combined criterion was designed to increase sensitivity while preserving specificity in identifying clinically meaningful familial enrichment.

Statistical Plan and Sample Size.

To identify the target subgroup, we estimated a 10% prevalence of enriched FHC patterns. Using a binomial exact calculation with a 95% confidence level and a margin of error of $\pm$ 5%, we determined that 175 patients were required. A minimum sample size of 180 patients was established to account for attrition.

Descriptive statistics were used to summarize the baseline characteristics of enrolled patients, including demographics, tumor histology, stage, smoking status, oncogene addiction profiles, and environmental exposures. FHC was characterized through the calculation of a weighted FHC score, integrating cancer diagnoses in first-degree relatives, age at onset, lung cancer occurrence, non-smoking status, and adjusting for family structure. The distribution of FHC scores were analyzed to identify patients in the top 10% percentile or the top 25% percentile with additional risk factors. Frequencies and proportions will be used for categorical variables, while medians and interquartile ranges will describe continuous variables. Analyses were conducted using R (R Core Team, 2021) and MedCalc® Statistical Software version 20.

3. Results

Study population

Between October 2023 and March 2025, a total of 388 consecutive patients with histologically confirmed NSCLC were enrolled across four Italian academic centers. Overall, 336 questionnaires were collected, resulting in an attrition rate of 14.4%.

Most patients were recruited at Fondazione Policlinico Universitario Campus Bio-Medico in Rome (n = 175, 52.1%), followed by IRCCS San Raffaele in Milan (n = 84, 25.0%), Azienda Ospedaliera Universitaria Città della Salute e della Scienza in Turin (n = 63, 18.8%), and IRCCS-IRST in Meldola (n = 14, 4.2%).

Baseline patients' characteristics are reported in Table 1. The median age at NSCLC diagnosis was 67 years (range 22–89), with 30 patients (8.9%) diagnosed at or before 50 years of age. The sex distribution was balanced (49.7% female, 50.3% male). Regarding smoking history, 10.7% were current smokers, 63.4% former smokers, and 25.9% had never smoked. Among smokers, the median pack-year exposure was 38.0 (IQR: 22.4–52.6), and 112 patients (33.2%) met the criteria for never or light smoking (defined as below the 10th percentile of pack-years).

Potential occupational exposure to carcinogens was reported in 18.1% of participants. Passive smoking exposure, defined as having one or both parents who smoked, was reported in 81.3% of patients, with 63.4% having one smoking parent and 17.9% both.

Histologically, adenocarcinoma was the predominant subtype (82.4%), followed by squamous cell carcinoma (10.1%) and other/undifferentiated subtypes (7.4%). The vast majority of patients weas diagnosed at advanced stage (stage IV: 76.5%), with only 3.0% at stage I. EGFR mutations and ALK rearrangements were detected in 24.4% and 11.9% of patients, respectively, with molecular data unavailable in 7.7% and 8.9% of cases.

A history of multiple primary malignancies was present in 27.7% of patients (n = 93), with tumor types including breast (16.1%), gastro-intestinal (19.4%), genitourinary, melanoma, lymphoma, and others.

Family History of Cancer.

Family history of cancer (FHC) data was available for all 336 patients and summarized in Table 2. Cancer in at least one parent was reported in 63.1% of cases (n = 212), with a median prevalence of 50% among parents (IQR: 0–50%). Among these affected parents, early-onset malignancy or multiple primary tumors were noted in 8.0%, lung cancer in 21.7%, and early-onset or never-smoker lung cancer in 0.5–2.4%.

Siblings were reported by 292 patients (86.9%), with a mean number of 2.4 siblings. Among these, 33.6% had at least one sibling with cancer, with a median cancer prevalence of 0% (IQR: 0–33.3%). Lung cancer was reported in 12.2% of affected siblings, and early-onset cancer in 26.5%.

Regarding offspring, 82.4% of patients (n = 277) had children, with a low cancer prevalence (6.1% reported at least one affected child). However, over half (52.9%) of affected offspring had early-onset or multiple malignancies.

Second-degree relatives (aunts/uncles) were reported by 95.2% of patients (mean: 7.1 per patient), with a crude cancer prevalence of 45.9% and median prevalence of 0% (IQR: 0–25%). Third-degree relatives (cousins) were available in 83.6% of cases, with a mean of 13 reported per patient and similar cancer prevalence (45.6%, median: 0%, IQR: 0–12.5%). In cases with partial or missing family history information, patients were conservatively classified as negative as per protocol.

FHC Score and Target Population Selection

To quantify familial cancer burden, we applied a structured, weighted FHC score incorporating first-, second-, and third-degree relatives (results summarized in Table 3). The mean overall FHC score was 0.43 (range: 0–1.48), with a median of 0.40 (IQR: 0.12–0.67). The 90th percentile threshold was established at 0.89 (95% CI: 0.83–0.96), and the 75th percentile threshold at 0.67 (95% CI: 0.62–0.71). When

Table 1

Patients' characteristics. Light smokers were defined as patients below the 10th percentile of pack-year distribution. Passive smoking exposure was defined as having at least one parent with a history of smoking. Multiple primary malignancies were defined as a history of at least one additional synchronous or metachronous malignant tumor distinct from non-small cell lung cancer. Among patients with multiple primary malignancies, 12 had three primary tumors and one patient had four primary tumors. Abbreviations: AJCC, American Joint Committee on Cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; H&N, head and neck; HCC, hepatocellular carcinoma; NOS, not otherwise specified; N° number; IQ range, interquartile range. *12 pts had 3 primary malignancies; 1 patient had 4 primary malignancies.

	Overall N° 336 (%)
Age, (years)	
Median (range)	67 (22.-89)
10th Percentile (95%CI)	51 (49—53)
Age ≤ 50 years at diagnosis	30 (8.9)
Sex	
Female	167 (49.7)
Male	169 (50.3)
Smoking status	
Current smokers	36 (10.7)
Former smokers	213 (63.4)
Never smokers	87 (25.9)
Smoking — Pack/Years (smokers only)	
Median (IQrange)	38.0 (22.4–52.6)
10th Percentile (95%CI)	9.5 (5.3–12.62)
Never smokers + light smokers	112 (33.2)
Potential work-related exposure to carcinogens	
No	276 (81.9)
Yes	61 (18.1)
Parental smoking behavior (passive smoking)	
No	50 (14.9)
One parent only	213 (63.4)
Both parents	60 (17.9)
Missing	13 (3.9)
Histology	
Adenocarcinoma	277 (82.4)
NOS/others	25 (7.4)
Squamous cell carcinoma	34 (10.1)
Stage at the enrollment (AJCC 8th edition)	
I	10 (3.0)
II	14 (4.2)
III	55 (16.4)
IV	257 (76.5)
EGFR mutation status	
No	228 (67.9)
Yes	82 (24.4)
Unknown	26 (7.7)
ALK translocation status	
No	266 (79.2)
Yes	40 (11.9)
Unknown	30 (8.9)
Multiple primary malignancies	
No	243 (72.3)
Yes*	93 (27.7)
Breast	15 (16.1)
Gastro-intestinal	18 (19.4)
Gynaecological	5 (5.4)
H&N	5 (5.4)
HCC	2 (2.2)
Hodkin Lymphoma	2 (2.2)
Non-H Lymphoma	5 (5.4)
Lung	6 (6.4)
Melanoma	4 (4.3)
Prostate	8 (8.6)
Renal cell carcinoma	6 (6.4)
Non-melanoma skin cancers	7 (7.5)
Soft tissue sarcoma	3 (3.2)
Thyroid	6 (6.5)
Urothelial	13 (13.9)

Table 2
Summary of the FHC data. Inserire spiegazioni delle abbreviazioni.

	Overall N° 336 (%)
Prevalence of cancer among parents[a]	
Crude rate (at least 1 parent)	212 (63.1)
Mean prevalence (range)	38.8 (0–100)
Median prevalence (IQrange)	50 (0–50)
Parents with cancer	**212 total**
Early-onset malignancy (or multiple)	17 (8.0)
Lung cancer	46 (21.7)
Lung cancer in never smoker	5 (2.4)
Early-onset lung cancer	1 (0.5)
Patients with siblings	
No	44 (13.1)
Yes	292 (86.9)
Number of siblings	
Mean (range)	2.4 (1–11)
Median (IQrange)	2 (1—3)
Prevalence of cancer among siblings[b]	**292 total**
Crude rate (at least 1 sibling)	98 (33.6)
Mean prevalence (range)	18.7 (0–100)
Median prevalence (IQrange)	0 (0–33.3)
Siblings with cancer	**98 total**
Early-onset malignancy (or multiple)	26 (26.5)
Lung cancer	12 (12.2)
Lung cancer in never smoker	–
Early-onset lung cancer	2 (2.0)
Patients with offspring	
No	59 (17.6)
Yes	277 (82.4)
Number of offspring	
Mean (range)	1.9 (1–4)
Median (IQrange)	2 (1—2)
Prevalence of cancer among offspring[c]	**277 total**
Crude rate (at least 1 sibling)	17 (6.1)
Mean prevalence (range)	3 (0–100)
Median prevalence (IQrange)	0 (0–0)
Offspring with cancer	**17 total**
Early-onset malignancy (or multiple)	9 (52.9)
Lung cancer	1 (5.9)
Lung cancer in never smoker	1 (5.9)
Early-onset lung cancer	1 (5.9)
Second-degree relatives (aunts and uncles)	
No	16 (4.8)
Yes	320 (95.2)
Number of aunts and uncles	
Mean (range)	7.1 (1–23)
Median (IQrange)	6 (4—9)
Prevalence of cancer among aunts/uncles[c]	**320 total**
Crude rate (at least 1 sibling)	147 (45.9)
Mean prevalence (range)	13.5 (0–100)
Median prevalence (IQrange)	0 (0–25)
Third-degree relatives (offspring of aunts/uncles only)	
No	55 (16.4)
Yes	281 (83.6)
Number of third-degree relatives	
Mean (range)	13 (1–60)
Median (IQrange)	11 (6—17)
Prevalence of cancer among third degree relatives[d]	**281 total**
Crude rate (at least 1 sibling)	128 (45.6)
Mean prevalence (range)	7.7 (0–100)
Median prevalence (IQrange)	0 (0–12.5)

[a] For 11 patients, FHC was not available for one of the two parents; for one patient, it was unavailable for both.

[b] for 2 patients, FHC was not available for siblings: All of these cases were considered negative.

[c] Among 78 patients, FHC data were partially missing for certain second-degree relatives (aunts and uncles); in accordance with study criteria, these cases were classified as negative.

[d] among 55 patients, FHC data were partially missing for certain third-degree relatives (offspring of aunts and uncles); in accordance with study criteria, these cases were classified as negative.

Table 3
FHC ratios and total FHC score results.

	Overall N° 336 (%)
FHC Ratio 1st degree	
Mean (range)	0.39 (0.1.44)
Median (IQrange)	0.35 (0–0.61)
FHC Ratio 2nd degree	
Mean (range)	0.03 (0–0.25)
Median (IQrange)	0 (0–0.06)
FHC Ratio 3rd degree	
Mean (range)	(0–0.15)
Median (IQrange)	0 (0–0.02)
Total FHC score	
Mean (range)	0.43 (0–1.48)
Median (IQrange)	0.40 (0.12–0.67)
90th quartile threshold (95%CI)	0.89 (0.83–0.96)
75th quartile threshold (95%CI)	0.67 (0.62–0.71)
Patients included ≥ 90th percentile threshold	33 (9.8%)
Patients included ≥ 75th percentile threshold	83 (24.7%)

stratifying patients according to these thresholds: 33 patients (9.5%) exceeded the 90th percentile; 22 patients (6.5%) were identified by the 75th percentile and fulfilled predefined clinical enrichment criteria (e.g., early-onset NSCLC, multiple malignancies, or never/light smoking with additional risk factors).

The combined target population for germline testing thus comprised 55 patients (16.4%) of the cohort, who demonstrated enriched FHC patterns suggestive of potential germline predisposition, identified as a target population for systematic referral to genetic counseling and germline testing.

Examples of family structures and FHC score computation

To illustrate the behavior and clinical interpretability of the FHC score across heterogeneous familial scenarios, representative examples of index cases are shown in Fig. 2 (panels A–D), with corresponding family tree reconstructions and stepwise score computation. These examples were selected to reflect distinct patterns of familial cancer aggregation and family structure. Collectively, the provided examples demonstrate the ability of the FHC score to capture clinically meaningful familial risk patterns across diverse family structures while accounting for differences in family composition.

4. Discussion

In this prospective observational study, we show that a structured and systematic assessment of family history identifies a clinically meaningful subset of patients with NSCLC enriched for familial cancer burden, representing approximately 16% of an unselected real-world population.

As mentioned, our findings address a relevant gap in knowledge [4] and extend previous heterogeneous and largely retrospective evidence by providing a prospective, standardized evaluation of familial cancer patterns in NSCLC. Rather than relying on binary definitions of family history, the FHC score captures gradients of familial cancer burden while accounting for family structure, allowing identification of enriched profiles that would otherwise remain unrecognized. Completion of the observational phase enabled definition of fixed, data-driven FHC cut-offs to be prospectively applied in the planned translational and multimodal analysis phase [4], designed to test the clinical utility of this framework for germline referral while minimizing circular reasoning (details provided **supplementary material**).

Emerging data on PGVs in lung cancer demonstrates substantial heterogeneity in reported prevalence and associations with family history. A large population based WES analyses suggest that a binary family history signal provides only limited enrichment for PGV carriage (e.g., 0.84% vs 0.71% for ATM, BRCA2 and TP53 in FH positive vs FH negative subjects) [6]. Conversely, in large clinical testing cohorts, up to ~

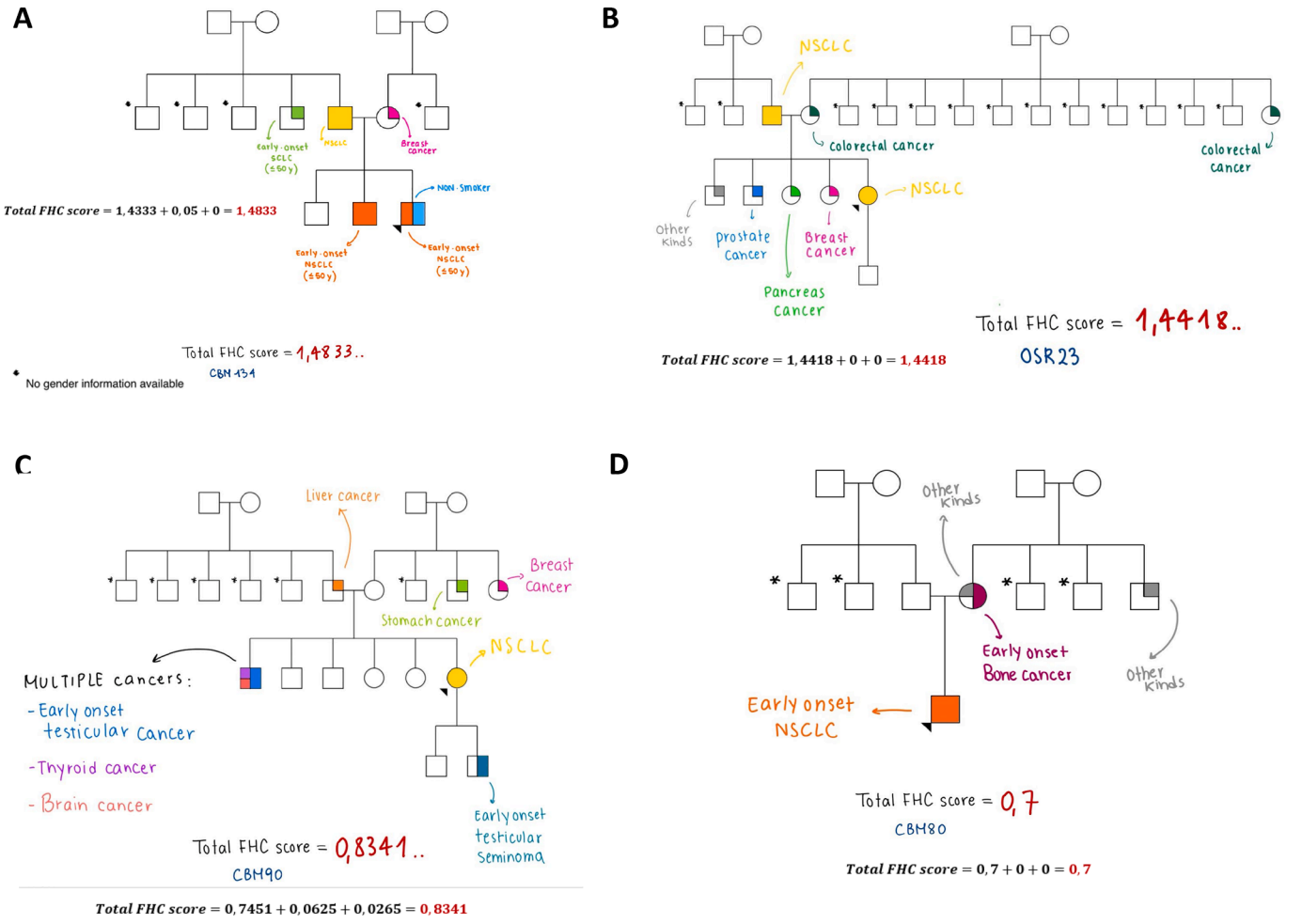

Fig. 2. Representative examples of index cases with corresponding family tree reconstructions and stepwise score computation. A (case CBM134) depicts a patient with early-onset non-small cell lung cancer, never smoker status, and a high burden of malignancies spanning first- and second-degree relatives, resulting in a total FHC score exceeding the 90th percentile. B (case OSR23) illustrates a patient with non small cell lung cancer and marked cancer aggregation confined to first-degree relatives, also reaching the ≥ 90th percentile threshold. C (case CBM90) represents a patient whose total FHC score exceeded the 75th percentile in association with additional clinical risk factors, including a sibling affected by multiple primary malignancies. D (case CBM80) exemplifies a patient with early-onset non-small cell lung cancer in whom apparent familial risk would be underestimated due to a reduced family structure; application of weighting corrections allowed identification of an enriched FHC profile above the 75th percentile threshold, supporting inclusion in the group of interest.

15% of patients undergoing germline profiling harbored PGVs, with enrichment seen in DNA damage response genes and other cancer susceptibility loci [7], supporting the need for more structured, quantitative family history frameworks to optimize referral for germline testing. In line with this, a recent whole-exome sequencing analysis from our group reported a heterogeneous spectrum of rare germline variants in patients with suspected familial lung cancer, without a dominant genetic driver [8].

Several clinical implications emerge from our findings. A structured evaluation of family history may help identify familial clustering effects that are not readily explained by shared smoking behavior or occupational exposures. In addition, by delineating a target population for genetic counseling, the FAHIC-Lung framework may contribute to a more efficient and sustainable implementation of germline testing strategies, especially in healthcare systems where universal germline sequencing is not feasible. Importantly, no universal surveillance recommendations (e.g., low-dose CT screening) are currently predefined within the FAHIC-Lung protocol, as evidence supporting systematic preventive strategies in this setting remains limited and requires dedicated investigation.

Our study has several limitations; despite the prospective design and the use of a dedicated questionnaire, family history data remain inherently dependent on patient recall and willingness to report information accurately. To mitigate this, patients were given time to collect information between study visits, and missing data were handled conservatively; however, residual recall bias cannot be excluded. The FHC questionnaire and composite score used in this study represent a newly developed framework and have not undergone prior external or outcome-based validation. Their development was motivated by the current lack of standardized and validated tools to guide referral for genetic counseling and germline testing in patients with non-small cell lung cancer. While the scoring system was conceptually validated by a clinical geneticist to ensure biological and clinical plausibility, formal validation against germline sequencing outcomes is beyond the scope of the present observational phase. Importantly, prospective clinical validation of this framework represents a core objective of the planned translational phase of the FAHIC-Lung study, which will assess the ability of the FHC score to enrich for pathogenic or likely pathogenic germline variants.

Additionally, the study population is derived from Italian academic centers and therefore predominantly includes patients of European ancestry, which may limit generalizability to other ethnic groups with different genetic backgrounds and cancer epidemiology. Furthermore, the requirement to complete a detailed questionnaire may have favored

the inclusion of patients who were younger or more motivated to participate. In addition, patients with better cognitive ability to recall and provide comprehensive family history information may have been overrepresented. This may partially explain the ~ 14% attrition rate and the observed enrichment of patients with oncogene-addicted tumors, early-onset disease, or never/light smoking status, while the study design, with a 4-week interval for questionnaire collection, may have led to the inclusion of a high proportion of patients with stage IV disease, a population that typically attends hospital more frequently. While this could influence prevalence estimates, it also reflects a real-world scenario in which patients most likely to benefit from genetic counseling may be those able to engage actively in detailed risk assessment processes.

Family history of cancer was assessed cross-sectionally, reflecting its intended use as a pragmatic, time-zero decision tool to support referral to genetic counseling in routine clinical practice. The study design does not include longitudinal follow-up of family members to capture incident cancers over time; however, this does not limit the applicability of the framework for its primary purpose, which is to inform referral at the time of patient evaluation. Family history is inherently dynamic, and repeat assessment over time may be clinically appropriate in selected cases if relevant changes in familial cancer occurrence emerge.

Familial aggregation of lung cancer may reflect not only inherited susceptibility but also clustering of shared environmental and behavioral risk factors, particularly smoking habits within families. Although detailed information on smoking behavior among relatives and passive smoking exposure was prospectively collected, and lung cancer in never smokers and early-onset lung cancer were weighted as higher-risk signals suggestive of inherited predisposition, residual confounding by shared smoking behaviors cannot be fully excluded. This highlights the importance of interpreting familial cancer aggregation within a multifactorial framework and supports the need for germline sequencing in the translational phase to disentangle inherited from shared environmental contributions.

In conclusion, the FAHIC-Lung observational phase demonstrates that a standardized and weighted assessment of family history may help identify a subset of patients with NSCLC enriched for familial cancer patterns. This framework represents a pragmatic and hypothesis-generating approach to support referral to genetic counseling, whose clinical utility will require prospective validation in the planned translational phase.

Authors' contributions.

All authors contributed to the publication according to the ICMJE guidelines for the authorship (study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision). All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study).

Availability of data and materials.

The dataset used for this study contains patient-level data that cannot be made available to third parties, although anonymized. Third party research proposals will be assessed by the study investigators and performed by the study team if accepted. Requests can be made to AC (a.cortellini@policlinicocampus.it).

Consent for publication

Not applicable.

Ethical declaration

The FAHIC-Lung study received approval from all relevant ethics committees, including the central IRB (Comitato Etico Territoriale Lazio AREA 2, protocol 27.23 CET 2 CBM, approved October 12, 2023), and was registered on ClinicalTrials.gov (NCT06196424).

Declaration of AI-assisted technologies in the writing process:

During the preparation of this work, the author(s) used ChatGPT (GPT-5) solely to improve the readability and clarity of the text. After using this tool, the author(s) thoroughly reviewed, verified and edited all content, and take full responsibility for the final version of the manuscript.

CRediT authorship contribution statement

Fabrizio Citarella: Writing – review & editing, Investigation, Data curation, Conceptualization. **Francesco M Venanzi:** Data curation. **Giulia Di Giovanni:** Writing – original draft, Visualization, Data curation. **Kazuki Takada:** Visualization, Validation. **Priscilla Cascetta:** Writing – review & editing, Visualization. **Pierfilippo Crucitti:** Writing – review & editing, Visualization. **Carla Lintas:** Writing – review & editing, Visualization, Validation. **Mattero Fiorenti:** Data curation. **Emanuele C Mingo:** Data curation. **Giulia La Cava:** Data curation. **Marco Russano:** Data curation. **Francesco Pantano:** Writing – review & editing, Visualization. **Bruno Vincenzi:** Writing – review & editing, Visualization. **Giuseppe Tonini:** Writing – review & editing, Validation. **Tiziana Vavalà:** Data curation. **Enrica Milanesi:** Data curation. **Sara Oresti:** Data curation. **Lucio Crinò:** Writing – review & editing, Data curation. **Angelo Delmonte:** Data curation. **Roberto Ferrara:** Writing – review & editing, Visualization, Conceptualization. **Massimo Di Maio:** Writing – review & editing, Visualization, Conceptualization. **Fiorella Gurrieri:** Visualization, Validation, Supervision, Conceptualization. **Alessio Cortellini:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Appendix A. Supplementary data

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