Critical Reviews in Oncology / Hematology 223 (2026) 105307

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The role of germline mutations in non-small cell lung cancer: A systematic review of emerging genetic drivers and clinical implications

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ARTICLE INFO

Keywords:
Non-small cell lung cancer
Germline mutations
Hereditary cancer predisposition
Precision medicine
Genetic counselling

ABSTRACT

Background: Lung cancer is the second most common malignancy and the leading cause of cancer-related mortality worldwide. While tobacco exposure remains the main risk factor, 15–20% of cases occur in never-smokers, suggesting a role for genetic predisposition. Although infrequent compared to somatic alterations, germline alterations may contribute to non-small cell lung cancer (NSCLC) susceptibility, with implications for risk assessment, targeted therapy, and family counselling.

Methods: A systematic review was conducted following PRISMA guidelines (PROSPERO ID:CRD420251081416). PubMed, SCOPUS, and Web of Science were searched up, for studies on germline mutations in NSCLC. Eligible articles reported prevalence, molecular characterization, or clinical relevance. Thirty-nine studies out of 5687 screened met inclusion criteria. Risk of bias was assessed using the Joanna Briggs Institute checklist.

Results: Germline mutations result overall rare in NSCLC. Most germline mutations in NSCLC involve genes participating in DNA damage repair and cell cycle control, including *ATM, BRCA1/2, TP53, PALB2, CHEK2,* and *EGFR*. Prevalence rates varied by gene, cohort characteristics, ethnicity, and histology with specific variants linked to increased lung adenocarcinoma risk, often in younger or never-smoker patients. Certain variants may predict sensitivity or resistance to target therapies.

Conclusions: Germline mutations constitute a minority of NSCLC cases but carry important prognostic, predictive, and preventive implications. Systematic germline testing in selected patients, particularly those with early-onset disease, strong family history, or tumor sequencing suggestive of hereditary variants, could guide precision oncology, enable targeted treatments, and facilitate familial risk management.

1. Introduction

Lung cancer is the second most common malignancy and remains the leading cause of cancer-related mortality worldwide, with an estimated global burden over millions of deaths annually (Sung et al. 2021).

Smoking is the primary risk factor, conferring a nearly tenfold increase in lung cancer risk compared to non-smokers. However, other environmental and occupational exposures, including air pollution, ionizing radiation, asbestos, and pulmonary disease, have also been implicated in lung cancer pathogenesis. While tobacco exposure accounts for the majority of cases, a significant proportion (15–20%) of lung cancer occurs in individuals without a known smoking history, suggesting that genetic predisposition plays a crucial role in disease susceptibility (O'Keeffe et al. 2018).

Molecular profiling is essential for the optimal clinical management of patients with non-small cell lung cancer (NSCLC). Worldwide, approximately 20–40% of individuals with advanced NSCLC harbour genomic alterations that are clinically actionable, though this proportion can vary based on many factors such as age, ethnicity, smoking history, tumor histology, and others (Jordan et al. 2017).

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https://doi.org/10.1016/j.critrevonc.2026.105307
Received 19 August 2025; Received in revised form 25 March 2026; Accepted 28 March 2026
Available online 31 March 2026
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These molecular alterations are prognostic and predictive of response to currently approved first-line therapies, making the use of targeted treatments mandatory in some cases (Mosele et al. 2020a; Hendriks et al. 2023).

A family history of lung cancer has been identified as a significant risk factor, particularly among individuals with two or more affected relatives (Lissowska et al. 2010). Notably, familial clustering of lung cancer is more pronounced in cases of early-onset disease (age <50 years), with first-degree relatives of patients with early-onset lung cancer exhibiting a higher likelihood of developing the disease compared to relatives of those with late-onset lung cancer (Rachtan et al. 2009). These findings underscore the potential contribution of inherited genetic factors to lung cancer susceptibility. Nevertheless, the majority of genomic alterations detected in NSCLC are described as somatic mutations (Pathak et al. 2025).

Despite increasing evidence supporting a hereditary component in lung cancer, the incidence of pathogenic germline mutations remains relatively low, aging from 4% to 21% among patients with NSCLC. Most studies investigating germline mutations in NSCLC have been single case reports, or series, with only a limited number of population-based studies reporting the prevalence of such mutations in affected individual (Parry et al. 2017; Mukherjee et al. 2022).

Given the growing interest in the genetic basis of lung cancer, a comprehensive understanding of germline variants could have significant clinical and therapeutic implications.

In this systematic review, we summarize current knowledge on the genetics of lung cancer susceptibility, focusing on the incidence of germline mutations, their clinical relevance, and potential therapeutic applications. All genes identified through the applied search strategy were included, rather than limiting the analysis to genes currently reported in clinical guidelines (Tung et al. 2024). By elucidating the hereditary components of lung cancer, we aim to highlight key biological insights and their implications for precision medicine strategies in lung cancer management.

2. Materials and methods

2.1. Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021). A protocol was developed and registered in PROSPERO (International Prospective Register of Systematic Reviews; ID: CRD420251081416).

PubMed, SCOPUS, and Web of Science were searched up, for studies on germline mutations in NSCLC, on July 15, 2025, and updated on January 10,2026 to include the most recent studies.

2.2. Eligibility criteria

Studies were considered eligible if they investigated germline mutations in patients with NSCLC.

Population: adult patients with a diagnosis of NSCLC.

Study designs included: retrospective or prospective clinical studies, preclinical studies (animal or in vitro models).

Study designs excluded: case reports, conference abstracts, narrative reviews, systematic reviews, or meta-analyses and studies not pertinent to the research question.

Language: only articles published in English were considered.

Primary outcomes: prevalence and spectrum of germline mutations reported in NSCLC.

Secondary outcomes: association of germline mutations with tumorigenesis, disease progression, familial risk, clinical characteristics (e.g., age, smoking status, histology), and therapeutic or prognostic implications.

2.3. Information sources and search strategy

A comprehensive literature search was performed in PubMed, SCOPUS, and Web of Science to identify available published articles on the role of germline mutations in lung cancer.

For PubMed, the search strategy was: "germline mutations" AND "lung cancer".

For SCOPUS and Web of Science, the search strategy was: "germline mutation" AND "lung cancer", limited to the following subject areas: Oncology, Biology, Chemistry, Chemistry Analytical and Medicinal, Cell Biology, Biochemistry Molecular Biology, Pathology, Gastroenterology Hepatology, Surgery, Medicine Research Experimental, Physiology, and Pharmacology. Given the substantial heterogeneity in terminology used in the literature, an additional analysis was conducted using alternative and complementary terms, including “polymorphism AND ”variant,” AND “genetic susceptibility,” AND “single nucleotide polymorphism,” AND “lung cancer.”

The use of “AND” between these terms was intended to focus the search on studies addressing all aspects, ensuring higher specificity and relevance and to reduce the retrieval of irrelevant studies while maintaining a sensitive and targeted search. Moreover, additional relevant studies were identified through manual research were included despite not been retrieved by the initial database research.

2.4. Selection process

Two authors (G.G. and M.S.) independently screened titles and abstracts using the online software Rayyan (https://www.rayyan.ai/). Full texts were retrieved for all records that met the inclusion criteria or when eligibility was uncertain. Disagreements were planned to be resolved by discussion with a third reviewer; however, the two authors were in full agreement at all stages, and a third reviewer was not required.

2.5. Data collection process

Data were extracted independently by the two reviewers into a predesigned Microsoft Excel form. Extracted information included study characteristics (author, year, design, sample size), patient population, germline mutation(s) investigated, and reported clinical and biological outcomes.

2.6. Risk of bias assessment

The risk of bias of the included studies was evaluated using the Joanna Briggs Institute (JBI) eight-item Critical Appraisal Checklist for Analytical Cross-Sectional Studies (Munn et al. 2015). For each study, the number of “Yes” responses was summed, and risk of bias was categorized as low (6–8 “Yes” responses), medium (4–5 “Yes” responses), or high (≤3 “Yes” responses). Among the 39 included articles, 15 (38.4%) were classified as low risk of bias, 17 (43.6%) as medium, and 7 (18%) as high risk of bias (Table 1 Supplementary).

Most of the studies included in this review were affected by small sample sizes, retrospective designs, and incomplete or inconsistent reporting of key outcomes, which may compromise the reliability and robustness of the results and limit their generalizability. These limitations should be considered when interpreting the findings.

3. Results

A total of 5687 records from three databases has been identified with the afore-mentioned search strategy, and 3520 were excluded before screening by automation tools. We independently screened by title and abstract 2167 records: 1020 for irrelevant content and 819 duplicates were excluded. Of the remaining 328 reports assessed for eligibility, 289 were excluded as they did not meet the predefined inclusion criteria. The

final records included for analysis were 39. The selection process is illustrated in Fig. 1. The list and characteristics of the included studies are presented in Table 2 Supplementary.

3.1. ATM

Ataxia-telangiectasia mutated (ATM) has been established as a moderate-penetrance risk gene for NSCLC. ATM is a serine/threonine protein kinase that serves as a regulator of the DNA damage response, specifically activated by DNA double-strand breaks. ATM phosphorylates numerous downstream targets that coordinate cell cycle checkpoints, DNA repair, and apoptosis (Shiloh and Ziv, 2013).

ATM mutations occurred in ~9% of adenocarcinomas and ~4% of squamous cell carcinoma based on The Cancer Genome Atlas cohorts (Thu and Yoon, 2024). A case-control study analysing germline whole-exome sequencing data from 1083 NSCLC adenocarcinoma patients and 7650 controls identified a significantly higher burden of rare deleterious variants (RDVs) in the *ATM* gene among adenocarcinoma patients, a finding replicated in an independent clinical cohort from the MSK-IMPACT study (Esai Selvan et al. 2020; Zehir et al. 2017).

Germline variants occur between 0.7% and 2% of NSCLC patients, with higher rates in adenocarcinomas. Furthermore, rs56009889, was observed at a higher frequency in adenocarcinoma cases within the Ashkenazi Jewish cohort (Esai Selvan et al. 2020). Individuals harbouring *ATM* RDVs may benefit from enhanced surveillance, early detection strategies, and chemoprevention to improve clinical outcomes (Esai Selvan et al. 2020).

A large-scale study of individuals undergoing multigene panel testing between 2015 and 2020 demonstrated that *ATM* loss-of-function and missense pathogenic (PV)/likely pathogenic variants (LPV) were more frequently identified in lung cancer cases compared to ethnically matched healthy controls further reported an odds ratio (OR) ranging from 4.68 to 5.50 for lung cancer in *ATM* variant carriers, reinforcing previous findings that *ATM* PV/LPVs are associated with increased lung cancer susceptibility (Laitman et al. 2022; Hall et al. 2021).

A large case-control study analysing 19053 lung cancer cases and 15446 healthy controls of European ancestry in a discovery phase, followed by a validation analysis with 4261 lung cancer cases and 4152 healthy controls, demonstrated that *ATM* rs56009889 significantly influenced lung cancer risk. This association was particularly evident in lung adenocarcinoma, with a stronger effect observed among women and never-smokers (Ji et al. 2018).

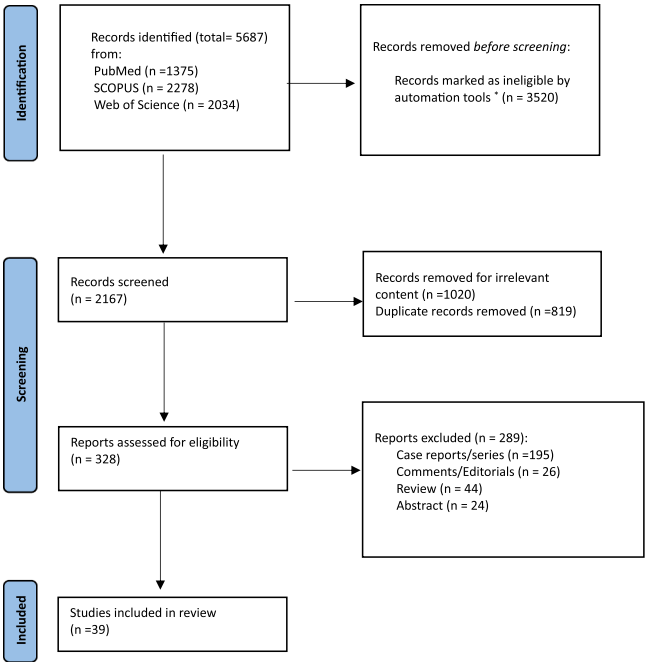

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Currently, several Ataxia Telangectasia and Rad3-related protein (ATR) inhibitors, are in various stages of clinical development (Hernandez-Martinez et al. 2023; Schmitt et al. 2017). These agents hold promises for targeted therapy, particularly in *ATM*-mutant NSCLC, and may enhance treatment efficacy when combined with immunotherapy or DNA-damaging agents although their role should be explored in germline ATM mutations.

3.2. BAP1

*BRCA*1-associated protein 1 (*BAP1*) is a tumor suppressor gene whose germline pathogenic variants are known to predispose to a hereditary cancer syndrome characterized by uveal melanoma, mesothelioma, renal cell carcinoma, and other malignancies (Shen et al. 2016). In the context of NSCLC, particularly lung adenocarcinoma, germline *BAP1* mutations appear to be rare, and current evidence suggests that *BAP1* does not represent a major inherited susceptibility gene for lung cancer. To date, only limited data are available on germline *BAP1* alterations in NSCLC, with most studies reporting very low prevalence. In an analysis of 257 NSCLC cases, only one tumor showed complete *BAP1* loss, indicating that both germline and somatic inactivation of *BAP1* are uncommon in lung cancer (Andrici et al. 2016). Nevertheless, this finding suggests that when germline *BAP1* alterations are present, they may contribute to tumor development through loss of tumor suppressor function (Kang et al. 2022).

From a biological perspective, *BAP1* plays a role in regulating tumor progression by interacting with *KEAP1* and modulating the *NRF2* pathway, thereby influencing oxidative stress responses, tumor cell migration, and apoptosis. Although these mechanisms have been mainly described in the context of somatic dysregulation, they provide a plausible framework for understanding how germline *BAP1* mutations, when present, could facilitate lung tumorigenesis.

Overall, while germline *BAP1* mutations do not appear to be a common inherited risk factor for NSCLC, their identification remains clinically relevant, particularly in patients with personal or family histories suggestive of *BAP1* tumor predisposition syndrome (Kobrinski et al., 2020). Further studies are needed to better define the contribution of germline *BAP1* variants to lung cancer susceptibility and to clarify their potential role in genetic counselling and personalized surveillance strategies.

3.3. BRCA 1/2

Germline mutations in the Breast Cancer Gene 1 and 2 (*BRCA1/2*), traditionally associated with hereditary breast and ovarian cancer, have been increasingly explored in NSCLC, particularly in lung adenocarcinoma. BRCA1 and BRCA2 are tumor suppressor genes that encode proteins essential for homologous recombination repair (HRR) of DNA double-strand breaks.

The carrier frequency of germline *BRCA1/2* mutations in Chinese NSCLC patients is reported to be 0.95%, which is significantly lower than the 7.2% observed in patients with hereditary breast and ovarian cancer (Hu et al. 2019; Xu et al. 2021). A study involving 6220 NSCLC patients found a pathogenic germline *BRCA* mutation prevalence of 1.03%, with *BRCA2* mutations (76.5%) being more common than *BRCA1* mutations (Remon et al. 2020).

Consistent with these findings, whole-genome sequencing study of NSCLC identified rare germline loss-of-function variants, predominantly in *BRCA2* and other cancer predisposition genes, in 5.29% of cases, with *BRCA2* promoter variants also significantly contributing to NSCLC risk (Wang et al. 2022).

Another study identified *BRCA1/2* variants in 5.3% of advanced

NSCLC patients, with confirmed pathogenic mutations found in 2.1% (Zhong et al. 2021). In a separate cohort of 640 lung adenocarcinoma samples, pathogenic *BRCA* mutations were found in 1.25% of cases (Zhong et al. 2021). The prevalence of *BRCA1/2* mutations is notably higher in patients diagnosed with NSCLC before the age of 50, and frameshift and nonsense mutations are the predominant mutations in these patients (Sanchis-Borja et al. 2022).

Additional rare *BRCA2* variants have been associated with an increased risk for lung squamous cell carcinoma (OR 3.3, 95% CI 1.1–9.3) (Esai Selvan et al. 2019).

These findings underscore the importance of *BRCA* mutations in lung adenocarcinoma and suggest that they are more commonly found in younger patients with advanced diseases. In terms of clinical significance, therapeutic strategies for NSCLC patients with germline *BRCA* mutations, especially those with *BRCA2* mutations, have shown promising results with the use of Poly ADP-Ribose Polymerase inhibitors (PARPi) such as olaparib and niraparib. Studies indicate that metastatic NSCLC patients with germline *BRCA1/2* mutations exhibit positive responses to PARPi, demonstrating promising objective response rate and prolonged progression-free survival (PFS) even after multiple lines of treatment (Ji et al. 2020; Arnon et al. 2023; Parisi et al. 2023).

The National Comprehensive Cancer Network recommends germline testing for pathogenic *BRCA1/2* mutations in patients with somatic tumor sequencing that reveals such mutations, which can guide recommendations for screening, preventive measures, and cascade testing for at-risk family members (Vlessis et al. 2020). Furthermore, patients with lung adenocarcinoma and concurrent *EGFR* mutations, along with germline *BRCA* mutations, have been observed to have significantly longer overall survival (OS) compared to those with *EGFR* mutations alone (Karachaliou et al. 2021).

In conclusion, while *BRCA1/2* mutations are not the primary drivers of lung cancer, they represent a subset of NSCLC patients, particularly those with adenocarcinoma, who may potentially benefit from targeted therapies such as PARPi. The growing recognition of these mutations, along with the identification of other genetic alterations, is crucial for personalizing treatment strategies and improving outcomes for these patients.

3.4. *CHECK2*

Checkpoint kinase2 *(CHEK2)* encodes a critical kinase that mediates cell cycle arrest and triggers apoptosis in response to DNA damage. Interestingly,*CHEK2 alterations* can confer a protective effect in the presence of persistent DNA damage, such as from tobacco exposure (Brennan et al. 2007).

Somatic alterations in *CHEK2***.** are uncommon in NSCLC but may impact DNA damage checkpoint signaling when present. Germline variants in *CHEK2***.** are generally rare and are not typically associated with increased lung cancer risk. Specifically, the *CHEK2* I157T variant has been associated with a reduced risk of lung squamous cell carcinoma, with a hazard ratio (HR) of 0.20 (95% (confidence interval) CI: 0.10–0.38) (Cybulski et al. 2008). While this variant is relatively common in Eastern European populations (with an allele frequency as high as 5%), it is rare among Western Europeans (Brennan et al. 2007).

A survey of NSCLC samples profiled by plasma next-generation sequencing revealed that 0.87% of cases (53 out of 6101) carried germline *CHEK2* variations. These alterations were predominantly amino acid substitutions (54.3%), followed by frameshift mutations (40.0%) and splice site mutations (5.7%). Notably, 41.4% of these cases harboured potentially actionable driver alterations, with the *KRAS* G12C mutation being the most frequent (Zhang et al. 2022).

3.5. *EGFR*

Epidermal Growth Factor Receptor (*EGFR*) plays a central role in NSCLC carcinogenesis by encoding a receptor tyrosine kinase that regulates cell proliferation, survival, and differentiation. Somatic alterations in *EGFR* are common drivers of lung adenocarcinoma, whereas germline variants are rare but clinically significant, occurring in approximately 0.1–1.2% of unselected NSCLC cases, with a population prevalence of 1 in 7500 individuals (Liu et al. 2023a; Gazdar et al. 2014).

The most extensively studied germline variant is the exon 20 substitution *T790M*, which functions as a "gatekeeper" by increasing the kinase domain's affinity for adenosine triphosphate (ATP), thereby competitively inhibiting the binding of first- and second-generation *EGFR* tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib. However, *T790M* alone exerts only weak oncogenic activity; it typically co-occurs with a second, somatically acquired activating *EGFR* mutation, most frequently *L858R* or exon 19 deletions, to achieve full oncogenic potential. This "two-hit" model is supported by findings that approximately 95% of *T790M* germline carriers with lung cancer harbour concurrent somatic *EGFR* driver mutations. The penetrance of *T790M* mutations is incomplete, with lung cancer developing in approximately 55% of germline carriers and in 52% of cases by age 60, indicating variable expressivity potentially modulated by environmental exposures or genetic modifiers such as *TP53* co-mutations or *EGFR Q787Q* polymorphisms (Pujol e Erich Eberhardt, 2024).

In addition to *T790M*, other *EGFR* germline variants such as *V843I, P848L, R776H/G, K757R, D1014N, L792F, G724S*, and *R831H*, have been increasingly reported, with variable oncogenicity and clinical relevance (Gabriel et al. 2024). *V843I*, which has been associated with constitutive receptor activation and *EGFR* destabilization, may be associated to secondary somatic mutations, such as *L861Q or L858R*, thus promoting tumorigenesis and contributing to TKI resistance (Matsushima et al. 2014). *P848L*, prevalent in certain Chinese NSCLC cohorts (~11% of *EGFR* germline variants), is intrinsically insensitive to *EGFR*-TKIs, with clinical studies demonstrating poor therapeutic outcomes (PFS of 78–120 days with erlotinib). *K757R*, observed in up to 35.7% of East Asian patients with germline *EGFR* alterations, is considered as a variant of uncertain significance (VUS) due to limited functional and clinical evidence (Lin et al. 2021; Lu et al. 2019; Yang et al. 2021a).

Population-specific prevalence patterns underscore the role of ethnic and geographic heterogeneity, with *T790M* more frequent in Western populations and other mutations such as *K757R, D1014N*, and *R831H* more prevalent in East Asian cohorts, suggesting population-specific risk alleles. Therapeutically, the presence of a germline *EGFR* variant poses significant treatment challenges. First- and second-generation TKIs are generally ineffective in germline mutation carriers unless accompanied by an activating somatic mutation (Lu et al. 2019).

Beyond *EGFR* itself, germline variants in modifier genes may influence *EGFR*-TKI efficacy; notably, the *USP36 rs3744797* (C>A, *K814N*) germline variant was associated with significantly shorter PFS in NSCLC patients treated with gefitinib or erlotinib, and mechanistically promotes *EGFR*-TKI resistance by upregulating USP36 expression(Guan et al. 2024).

In addition, a germline missense polymorphism in *FOXM1* (*rs3742076,* A>G*, S628P*), was significantly associated with shorter PFS in both exploratory and validation cohorts of *EGFR*-mutant NSCLC patients treated with gefitinib, and functionally conferred TKI resistance by enhancing *FOXM1* protein stability, activating Wnt/β-catenin signalling through direct interaction with β-catenin (Guan et al. 2022).

Third-generation TKIs such as osimertinib, developed specifically to overcome *T790M*-mediated resistance, have demonstrated promising efficacy. Real-world and prospective data from multiple cohorts have shown that first-line osimertinib in advanced-stage *EGFR*-mutant NSCLC with germline *T790M* variants yields a median progression free survival ranging from 16.9 to 20.4 months, and median OS up to 82 months, outcomes comparable to somatic *EGFR* mutations outcomes (Pan et al. 2024).

Nevertheless, resistance mechanisms remain a concern, particularly

in mutations like *P848L* or compound mutations involving multiple kinase domain variants. Importantly, plasma-based next generation sequencing (NGS), widely adopted for non-invasive tumor genotyping, can incidentally detect germline variants, necessitating confirmatory testing using matched peripheral blood mononuclear cells and subsequent genetic counselling (Hu et al. 2017).

In conclusion, germline *EGFR* variants, particularly *T790M*, represent a distinct subset of NSCLC that should be widely studied. Germline testing and genetic counselling when high allele fractions or *T790M* is found at baseline could become recommended in the future even if standardized germline testing guidelines are needed.

3.6. PALB2

Partner And Localizer of *BRCA2* **(*PALB2*)**, a crucial gene in the homologous recombination repair (HRR) pathway, has been associated with the effectiveness of platinum-based chemotherapy, immunotherapy, and PARPi in various cancers (AACR Project GENIE Consortium, 2017).

PALB2 is a tumor suppressor gene that serves as the molecular scaffold linking BRCA1 and BRCA2 in the homologous recombination (HR) DNA repair pathway. Somatic alterations in *PALB2* are relatively uncommon in NSCLC, whereas germline variants are even rarer, although lung cancer appears to have one of the highest overall mutation rates among all cancers (~1.8%). In a comprehensive NGS study of 5227 NSCLC patients, *PALB2* variants were detected in 4.76% of cases, comprising 3.1% germline and 1.66% somatic variants. Somatic mutations were associated with significantly higher tumor mutation burden compared to germline mutations, though no differences were observed in Programmed death Ligand 1 PD-L1 expression or microsatellite instability(Zhang et al. 2021).

Data from several cohorts (Rizvi2018, OAK, and POPLAR) revealed no significant difference in PFS or OS between *PALB2*-mutated (including both germline and somatic) and *PALB2* wild type NSCLC patients undergoing immunotherapy.

3.7. PARK2

Parkinson disease protein 2 *(PARK2)* is a tumor suppressor gene involved in cell cycle regulation and mitochondrial quality control and has been implicated in carcinogenesis across multiple tumor types. In NSCLC, somatic alterations of *PARK2* appear to be infrequent while germline are less than 2%. An analysis of 267 primary lung adenocarcinomas and 39 lung adenocarcinoma cell lines identified heterozygous germline exonic deletions in five patients, while loss of heterozygosity at the *PARK2* locus was observed in 11.6% of cases (Iwakawa et al. 2012).

Interestingly, homozygous *PARK2* inactivation was absent in primary tumors, including those harbouring germline mutations, but was detected in 15% of cell lines. These findings suggest that somatic *PARK2* mutations are rare or non-existent in the development of lung adenocarcinoma. While germline *PARK2* mutations may contribute to lung adenocarcinoma progression, they do not appear to be involved in the initial onset of the disease (Iwakawa et al. 2012).

Furthermore, *PARK2* rare alterations, such as *R275W*, have been linked to familial lung cancer, showing a large effect size (OR 5.24, 95% CI 1.33–15.00), possibly contributing to the heritability of lung cancer. Studies suggest that this germline *PARK2* mutations may be more common in patients with early-onset lung cancer underscoring the potential role of *PARK2* in early lung cancer development (Jove et al. 2023).

3.8. TP53

Tumor Protein p53 *(TP53)* germline mutations are strongly associated with an increased risk of various cancers, including NSCLC, particularly in individuals with Li-Fraumeni syndrome (LFS). Routine NGS of NSCLC often uncovers PV/LPV, especially in *TP53*. However, since *TP53* alterations in tumors are more commonly somatic rather than germline (≃1%), germline testing for Li-Fraumeni syndrome (LFS) is not recommended based solely on a *TP53* variant in an NSCLC (Sorscher, 2024).

Several studies have highlighted the influence of *TP53* germline variants on lung cancer risk, particularly in younger individuals and those with a family history of cancer. An analysis of over 29000 cases from the International Agency for Research on Cancer *TP53* Database and 7893 cancer cases from cBioPortal revealed that all *TP53* mutations are most commonly missense mutations, with hotspots at codons 248, 273, 175, and 245 for somatic mutations, and 337 and others in exons 9–10 for germline mutations. These mutations significantly affect survival and disease-free survival times in lung adenocarcinoma, among other cancers (Li et al. 2019).

In a study involving 738 cancers from 45 families with *TP53* germline variants, lung cancer was found to develop at much younger ages than in the general population, highlighting the increased risk for these individuals. Lung cancer, along with sarcomas, breast cancer, and leukemias, is typically associated with LFS (Zhang et al. 2000a). Furthermore, smoker patients with germline *TP53* mutations have a significantly higher risk of developing lung cancer. Specifically, smoker mutation carriers had more than three times the risk of lung cancer compared to non-smokers (Hwang et al. 2003).

Germline *TP53* mutations are also linked to an earlier onset of lung cancer compared to sporadic cases, with a significantly younger median age of diagnosis in mutation carriers. This trend is especially prominent in patients with LFS, where cancer onset can occur during childhood or early adulthood, underscoring the need for genetic counselling and early surveillance (Zhang et al. 2000b). In a study of 270 patients with *TP53* germline variants, lung cancer was one of the most common cancers associated with these mutations, particularly in male patients. The median age of diagnosis for patients with pathogenic/likely pathogenic *TP53* germline variant was significantly younger (31 years) compared to those without the mutation (53 years), with mutations occurring most frequently at codons 175 and 248 (Tian et al. 2022).

Overall, *TP53* germline mutations are a critical factor in lung cancer risk, particularly for individuals with a genetic predisposition. Further exploration in clinical settings is needed for early detection, risk assessment, preventive strategies but also as a predictor of response to treatments.

3.9. Other relevant mutations

The Kirsten rat sarcoma virus oncogene homolog (*KRAS)* variant (*rs61764370*) is a naturally occurring genetic change found in the germline, specifically in a non-coding part of the *KRAS* oncogene called the 3′ untranslated region. This variant sits within a sequence that matches a microRNA called let-7, which normally helps control *KRAS* gene activity by binding to it and lowering KRAS protein production. The variant changes a T to a G, which stops let-7 from binding properly. As a result, *KRAS* mRNA is less suppressed, leading to higher *KRAS* protein levels. This mechanism was first identified as a factor that increases the risk of NSCLC (Uvirova et al. 2015).

Found in 13.2% of NSCLC samples as the heterozygous TG genotype, this germline variant operates independently of somatic *KRAS* mutations and is less frequent in tumors with acquired *EGFR* or *KRAS* mutations (Reita et al. 2022). Despite its non-coding nature, the variant induces a "*KRAS*-addicted" gene expression signature in tumors, likely due to dysregulated let-7-mediated control. Clinically, the variant shows paradoxical therapeutic implications: unlike somatic *KRAS* mutations that confer resistance to cetuximab, *KRAS*-variant in NSCLC patients exhibit improved PFS and OS with cetuximab-based regimens, as demonstrated in the RTOG 0522 trial, where the variant was found in approximately 16% of patients and associated with a significant, time-dependent survival benefit. However, in the RTOG 0617 study, OS

rates were similar between variant and non-variant groups, though a time-dependent cetuximab effect persisted in variant carriers. These findings underscore how germline regulatory single-nucleotide polymorphism like the *KRAS* variant can influence both cancer risk and treatment response through miRNA-mediated oncogene dysregulation (Uvirova et al. 2015).

Anaplastic lymphoma kinase *(ALK)* rearrangements are somatic genomic alterations found in approximately 3–5% of patients with NSCLC, and they play a significant role in guiding targeted therapy (Chia et al. 2014). In contrast, germline mutations in *ALK* are far less understood, with limited data available regarding their prevalence and clinical significance. A large retrospective analysis involving 36,813 unselected lung cancer patients who underwent somatic mutation testing identified germline *ALK* mutations in only 22 individuals. Importantly, all detected germline variants were classified as variants of uncertain significance, highlighting the need for further research to clarify their potential role in cancer predisposition and progression (Yang et al. 2021b).

Serine/threonine kinase 11 (STK11) (also known as *LKB1)*, is a tumor suppressor gene that plays a critical role in the regulation of cellular metabolism, polarity, and apoptosis. Somatic mutations in *STK11* are observed in approximately 15–30% of lung adenocarcinomas. Germline *STK11* mutations are the genetic basis of Peutz-Jeghers Syndrome, a rare hereditary cancer predisposition syndrome. (Lim et al. 2003).

Germline mutations in mismatch repair (MMR) genes associated with Lynch syndrome are detected in approximately 0.5% of lung cancer patients; however, these tumors typically lack microsatellite instability and do not show loss of MMR protein expression, suggesting a sporadic origin rather than Lynch syndrome tumorigenesis. Accordingly, lung cancer is not considered part of the classical Lynch syndrome tumor spectrum. The MMR/MSI testing is not part of biomarker analysis for NSCLC, although comprehensive NGS panels can detect both somatic alterations and germline variants simultaneously, potentially identifying Lynch syndrome carriers incidentally (Sun et al. 2019).

MUTYH (MutY DNA glycosylase homolog) is a base excision repair gene that encodes an adenine DNA glycosylase responsible for removing adenine bases mispaired with 8-oxo-7,8-dihydroguanine (8-oxoG). Germline MUTYH pathogenic variants occur in approximately 1.1–1.6% of NSCLC patients, making MUTYH the most frequently detected germline alteration in lung cancer across multiple large cohorts. Importantly, MUTYH variants are associated with increased lung cancer risk, particularly among never smokers and individuals who do not meet current screening criteria (Govindan et al. 2025; Trendowski et al. 2025).

4. Discussion

This systematic review highlights the growing role of germline mutations in lung cancer susceptibility and its potential impact on cancer-specific survival. Although smoking remains the main risk factor, growing evidence indicate that germline mutations may contribute to lung cancer pathogenesis and hold clinical significance in a subset of patients.

Our analysis confirms that most germline mutations identified in lung cancer affect genes involved in DNA repair and cell cycle regulation, such as *ATM*, *TP53, BRCA2, PALB2* and *CHEK2*.

The inherited dysfunction of these genes compromises genomic stability, thereby increasing susceptibility to tumorigenesis, particularly among never-smokers and younger individuals (Citarella et al. 2024; Laguna et al. 2025).

According to the 2022 recommendations from the European Society of Medical Oncology (ESMO) Precision Medicine Working Group, germline genetic testing should be considered when tumor NGS identifies a mutation with a germline conversion rate exceeding 5%, indicating a high probability of hereditary origin. Furthermore, the Working Group defined a subset of "most actionable" genes, including *BRCA1, BRCA2,* and *MLH1*, for which germline-focused analysis is recommended irrespective of tumor type (Kuzbari et al. 2023).

Notably, *BRCA* mutations were initially classified as tier IIIA in the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) for non-squamous NSCLC. However, the latest ESMO recommendations on the use of NGS in metastatic cancer no longer include *BRCA1* and *BRCA2* among the list of ESCAT-defined actionable mutations for NSCLC, reflecting the ongoing evolution of evidence and consensus (Mosele et al. 2020b; Mosele et al. 2024).

Although rare, germline *EGFR* mutations, such as the T790M variant, plays a possible role on cancer susceptibility. Patients carrying these mutations, particularly those with a positive family history, could be referred for genetic counselling. However, the evidence regarding the differential therapeutic efficacy of *EGFR* inhibitors in germline versus somatic contexts remains limited and inconclusive (Liu et al. 2023b; Tung et al. 2024).

Germline mutation detection is described only in small-scale studies and the lack of routine germline testing, result in underdiagnosis and limited generalizability (Shukuya e Takahashi, 2019).

The INHERITY-LC trial, a prospective multicenter study, enrolled 145 NSCLC patients selected based on criteria such as young age, family history of NSCLC, and the presence of somatic mutations. Germline testing via NGS revealed a 10% prevalence of germline mutations, predominantly involving DNA damage repair genes (Zurera et al. 2025).

Clinically, identifying germline mutations has implications beyond risk stratification. Certain mutations may serve as predictive or prognostic biomarkers and necessitate familial surveillance. For example, germline *BRCA2* mutations have been associated with increased sensitivity to platinum-based chemotherapy and PARPi, treatments that are well-established in other cancer types and are now being investigated in NSCLC. Similarly, *ATM* deficiency may potentiate responsiveness to immunotherapy.

This review also highlight the heterogeneity of germline mutation prevalence across populations, which may reflect ethnic, geographic, and environmental variability, as well as selection bias in future clinical trials (Farinea et al. 2023).

A thorough understanding of the heterogeneity in germline mutation prevalence can help guide genetic counselling, including which patients should undergo germline testing, how test results may inform targeted therapy, and the development of population-specific screening strategies. For example, *T790M* germline variants are more frequent in Western populations, whereas other *EGFR* germline variants, such as *K757R, D1014N, and R831H*, are predominantly observed in East Asian cohorts (Lu et al. 2019).

Comprehensive genetic profiling can uncover hereditary risk in patients without a known family history or presenting with early-onset disease, facilitating timely surveillance and preventive measures for both patients and their relatives (Fig. 2).

The integration of germline testing into precision oncology frameworks offers a promising avenue for risk assessment, early detection, and individualized therapy. NGS enables high-throughput, accurate profiling of both germline and somatic alterations from tissue and liquid biopsies. Moreover, whole-genome and whole-exome sequencing allow for the identification of rare or novel variants and the detection of dual germline mutations, which may be missed (Mandelker et al. 2017; Dos Santos et al. 2022).

Indeed, tissue-based comprehensive genomic profiling identified germline mutations in 6.8% of a large NSCLC cohort, and in a separate large retrospective lung cancer cohort, germline mutations were detected in 14.9% of patients, with a similar prevalence among individuals without a family history or personal history of other cancers (Mezquita et al. 2020; Govindan et al. 2025; Sorscher et al. 2023).

Nevertheless, several challenges persist, including the interpretation of variants of uncertain significance, limited access to testing, and the absence of standardized clinical guidelines. International guidelines will have to help clinicians to prevent genomic misinterpretation through the

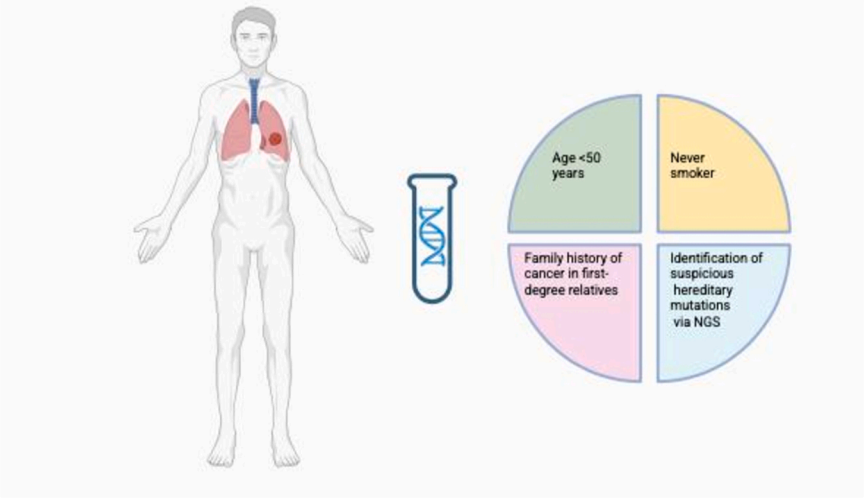

Fig. 2. Potential germline test criteria access for patients with lung cancer. Abbreviations: NGS: Next generation sequencing Created by the authors using BioRender.com, accessed on 12 July 2025.

development of clinical decision support tools and standardized protocols for variant interpretation.

We believe that in the future genetic counselling may be included into NSCLC germline management in clinical practice to ensure informed decision-making in multidisciplinary collaboration among oncologists, geneticists, pathologists, and other specialists (Fig. 3).

This systematic revision has several strengths. This is, to our knowledge, the first systematic revision on NSCLC germline mutations. A comprehensive literature search was conducted excluding case reports and including all relevant data on this unexplored theme. The main limitations are the heterogeneity of the studies included in terms of study design, populations and outcomes, limiting the possibility of a consistent quantitative synthesis.

The detection of germline alterations in NSCLC requires a structured approach to genetic counselling and testing. Referral for genetic counselling might be considered when tumor-only NGS identifies pathogenic or likely pathogenic variants in genes associated with hereditary cancer predisposition, particularly DNA damage repair genes such as *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and *TP53*, or when variants are detected at high allele frequencies suggestive of germline origin. Potential additional triggers include early-onset disease, a relevant personal or family cancer history, multifocal tumors, or the identification of rare variants with known hereditary relevance, such as germline *EGFR* T790M.

5. Conclusion

Although germline mutations account for a minority of lung cancer cases, their identification has possible implications for risk assessment,

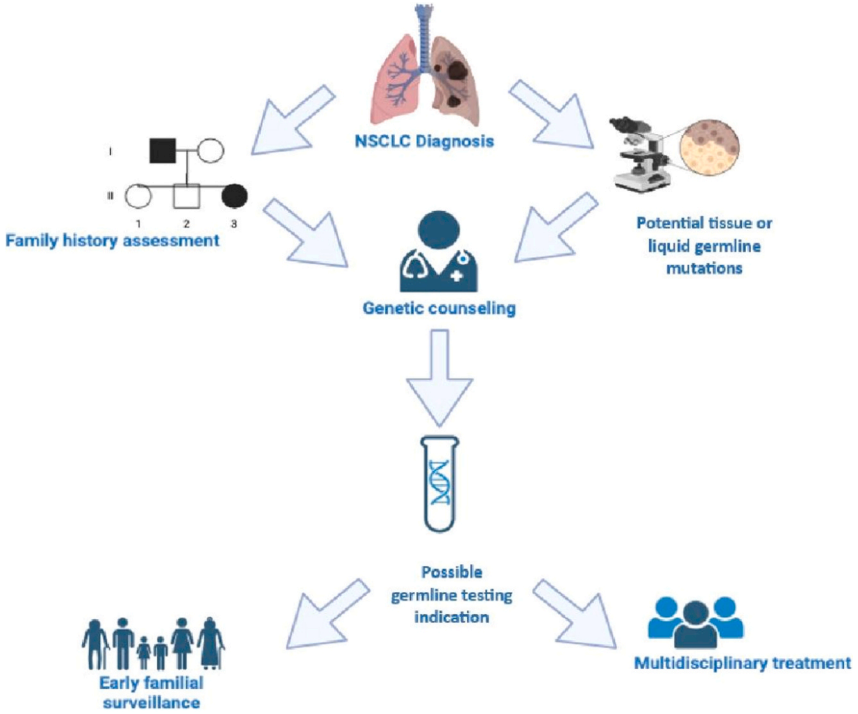

Fig. 3. Integrating Genetic Counselling and Multidisciplinary Care in NSCLC. Abbreviations: **NSCLC:** non-small cell lung cancer. Created by the authors using BioRender.com, accessed on 12 July 2025.

early detection, and personalized therapy. Incorporating germline genetic profiling into the management of selected patients could potentially enable tailored surveillance and intervention strategies, possibly benefiting both patients and their families. Continued research and the expansion of genomic NGS profiling screening are essential to fully realize the potential of germline genetics in improving lung cancer outcomes.

Author contributions

Gabriella Gentile: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft, **Alain Gelibter:** Formal analysis, Funding acquisition, Investigation, Supervision, Validation, **Laura De Marchis:** Formal analysis, Investigation, Supervision, Validation, **Laura Pappalardo:** Data curation, Investigation, Resources, Camilla Capasso: Data curation, Investigation, Resources, **Raffaele Giusti:** Formal analysis, Methodology, Supervision, Visualization, **Andrea Botticelli:** Methodology, Supervision, Validation, Visualization, **Federica Mazzuca:** Funding acquisition, Supervision, Visualization, **Daniele Santini:** Funding acquisition, Supervision, Visualization, **Marco Siringo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – review and editing

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2026.105307.

Data availability

This study is based exclusively on previously published data. All data analyzed during this study are included in the published articles cited in the reference list.

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