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Research article

# Worldwide analysis of actionable genomic alterations in lung cancer and targeted pharmacogenomic strategies

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A B S T R A C T

Based on data from the Global Cancer Statistics 2022, lung cancer stands as the most lethal cancer worldwide, with age-adjusted incidence and mortality rates of 23.6 and 16.9 per 100,000 people, respectively. Despite significant strides in precision oncology driven by large-scale international research consortia, there remains a critical need to deepen our understanding of the genomic landscape across diverse racial and ethnic groups. To address this challenge, we performed comprehensive *in silico* analyses and data mining to identify pathogenic variants in genes that drive lung cancer. We subsequently calculated the allele frequencies and assessed the deleteriousness of these oncogenic variants among populations such as African, Amish, Ashkenazi Jewish, East and South Asian, Finnish and non-Finnish European, Latino, and Middle Eastern. Our analysis examined 117,707 variants within 86 lung cancer-associated genes across 75,109 human genomes, uncovering 8042 variants that are known or predicted to be pathogenic. We prioritized variants based on their allele frequencies and deleterious scores, and identified those with potential significance for response to anti-cancer therapies through *in silico* drug simulations, current clinical pharmacogenomic guidelines, and ongoing late-stage clinical trials targeting lung cancer-driving proteins. In conclusion, it is crucial to unite global efforts to create public health policies that emphasize prevention strategies and ensure access to clinical trials, pharmacogenomic testing, and cancer research for these groups in developed nations.

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**Abbreviations**

| | |
|---|---|
| WHO | World Health Organization |
| GLOBOCAN | Global Cancer Statistics |
| PGx | Pharmacogenomics |
| TCGA | The Cancer Genome Atlas |
| TARGET | Therapeutically Applicable Research to Generate Effective Treatments |
| gnomAD | Genome Aggregation database |
| CGI | Cancer Genome Interpreter |
| CADD | Combined Annotation-Dependent Depletion |
| FDR | False discovery rate |
| GO | Gene ontology |
| KEGG | Kyoto Encyclopedia of Genes and Genomes |
| HP | Human phenotype ontology |
| PharmGKB | The Pharmacogenomics Knowledge Base |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| ESMO | European Society for Medical Oncology |
| NCCN | National Comprehensive Cancer Network |
| FDA | The US Food and Drug Administration |

## 1. Introduction

Lung cancer consists of lethal and aggressive tumors caused by uncontrolled cell division in the lungs [1]. This heterogeneous malignancy emerges from an intricate interaction of biological processes, ethnic background, epigenetic modifications, driver mutations, environmental exposures, and disruptions in protein signaling pathways [2]. According to the Global Cancer Statistics (GLOBOCAN 2022) report by the International Agency for Research on Cancer (IARC) under the World Health Organization (WHO), lung cancer holds age-adjusted incidence and mortality rates of 23.6 and 16.9 per 100,000 people worldwide, respectively [3].

Since the inception of the Human Genome Project in 1990, rapid technological advancements have revolutionized the field of omics sciences, culminating in the full sequencing of the human genome by 2022. This breakthrough has generated an enormous volume of data and knowledge, greatly enhancing both basic and clinical research [4,5]. The development of next-generation sequencing technologies has played a critical role in unrevealing the molecular underpinnings of lung cancer, leading to substantial progress in identifying cancer driver genes [6,7], germline mutations [8], mutations in non-coding regions and coding [9–13], druggable proteins [14,15], drug resistance [16], pharmacogenomics (PGx) strategies [17–20], and the application of artificial intelligence in cancer research [21,22].

Recent findings suggests that individuals with the same type of cancer may respond differently to standard treatments [23,24]. Precision oncology aims to address these variations by offering customized treatment to individual patients, ensuring that the right drug, at the correct dosage, is administrated to the right patient, considring their genetic and ethnic background [17,25]. A key objective in cancer research is to identify the most prevalent actionable genomic alterations within the lung cancer variome in healthy populations, thereby informing the development of preventive measures and advancing therapeutic innovations, alongside the implementation of clinical pharmacogenomic guidelines [26].

Customizing drug development based on an individual's multi-omics profile can enhance treatment efficacy while reducing the risk of adverse effects [18]. However, despite ongoing efforts to increase diversity in cancer research, many studies have excluded participants from diverse ethnic backgrounds [27]. Notably, prominent cancer genomics programs, such as The Cancer Genome Atlas (TCGA), have been predominantly composed of individuals of Caucasian descent (91.1 %) [27,28], highlighting a significant barrier to advancing pharmacogenomics in developing regions. To bridge this gap, we conducted integrated *in silico* analyses and data mining to pinpoint the most frequent actionable genomic alterations within the lung cancer variome, calculated their allele frequencies and deleteriousness scores across diverse populations, and prioritized strategies in precision oncology.

## 2. Methods

### 2.1. Epidemiology of lung cancer

The Global Cancer Observatory (https://gco.iarc.fr/), an interactive online platform developed by the IARC, offers comprehensive statistics on cancer incidence and mortality. Utilizing the most recent update from GLOBOCAN 2022, we analyzed and ranked countries based on their lung cancer incidence and mortality rates [3].

### 2.2. Genes driving lung cancer

IntOGen (Integrative OncoGenomics) (https://www.intogen.org) is a robust database that identifies genes driving cancer through

extensive analysis of mutations across various tumor genomes [29]. This bioinformatics tool incorporates data from top-tier cancer genomic databases like TCGA and the Catalogue of Somatic Mutations in Cancer (COSMIC) [30,31]. The study focused on 86 lung cancer driver genes, selected due to their high mutational frequency in cancer cohorts. These genes are crucial for key cellular processes involved in lung cancer, including DNA repair, cell cycle control, and signal transduction. IntOGen employs seven different methods to detect these mutational drivers in lung cancer, such as dNdScv [32], CBaSE [33], MutPanning [34], OncodriveCLUSTL [35], HotMAPS [36], smRegions [29], and OncodriveFML [37]. The identified genes were categorized into various functional groups, including oncogenes [38], tumor suppressor genes [38], kinase genes [39,40], DNA-repair genes [41,42], RNA-binding proteins [43], cell cycle genes [44], metastatic genes [45], and cancer immunotherapy genes [46].

### 2.3. The oncogenic variome of lung cancer

The oncogenic variome was identified through a two-step process. Initially, 117,707 insertion/deletion and single nucleotide variants associated with 86 lung cancer-driving genes were extracted from the Genome Aggregation Database (gnomAD v3.2.1) (https://gnomad.broadinstitute.org/), using the complete human genome sequence GRCh38/hg38 as a reference [5,47,48]. Following this, the tumorigenic potential of these variants was evaluated using the OncodriveMUT, which calculates the functional impact score for each mutation, particularly focusing on those that provide a growth advantage to cancer cells, and boostDM, which assesses the oncogenic potential through *in silico* saturation mutagenesis. Both machine learning-based methods are integrated into the Cancer Genome Interpreter (CGI) platform (https://www.cancergenomeinterpreter.org) [49,50].

### 2.4. Lung cancer variome deleteriousness scores

After predicting the tumorigenic potential of the oncogenic variome, we assessed the deleteriousness of annotated and predicted mutations in genes driving lung cancer using the Combined Annotation-Dependent Depletion (CADD) v1.4 tool. CADD evaluates the impact of insertion/deletion and single nucleotide variants by analyzing 60 genomic features [51] and encompasses several annotations by comparing simulated variants and natural selection [52]. The severity of the lung cancer variome was classified as follows: very high with a deleteriousness CADD score of 30–50, high from 25 to 30, medium from 15 to 25, low from 10 to 15, and very low from 0 to 10.

### 2.5. Functional enrichment analysis

Enrichment analysis is used to interpret node sets derived from high-throughput omics technologies [53–56]. In this context, we conducted a functional enrichment analysis on lung cancer-driving genes that carry either known or predicted oncogenic variants. The complete set of cancer-driver genes served as the background set [29,31,38]. The analysis was performed with the g:Profiler tool (https://biit.cs.ut.ee/gprofiler/gost) [57] to identify significant terms (Benjamini-Hochberg, false discovery rate (FDR) $q < 0.001$) related to biological processes in Gene Ontology (GO) [58], signaling pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG) [59], Reactome [60], and WikiPathways [61]. We then manually curated the significant pathways relevant to lung cancer.

### 2.6. Allele frequencies across diverse ethnic backgrounds

The gnomAD database is a large-scale resource offering genomic data from a diverse range of populations [48]. The v3.1.2 dataset, aligned with GRCh38/hg38, includes genomic information from 75,109 unrelated individuals representing diverse ethnic backgrounds. Our research focused on analyzing allele frequencies of the lung cancer variome across nine global populations. These groups comprise 34,029 European non-Finnish individuals, 20,744 African individuals, 7647 Latino individuals, 5316 European Finnish individuals, 2604 East Asian individuals, 2419 South Asian individuals, 1736 Ashkenazi Jewish individuals, 456 Amish individuals, and 158 Middle Eastern individuals [47,48].

### 2.7. Clinical pharmacogenomics guidelines

One of the most specialized resources edicated to collecting, curating, and sharing information on how genetic variations influence drug responses, offering guidance on the clinical application of pharmacogenomics, is The Pharmacogenomics Knowledge Base (PharmGKB) (https://www.pharmgkb.org/) [62,63]. This database compiles data from several sources, including the European Society for Medical Oncology (ESMO), the Canadian Pharmacogenomics Network for Drug Safety, the Clinical Pharmacogenetics Implementation Consortium (CPIC) [66,67], the Royal Dutch Association for the Advancement of Pharmacy [64], and the National Comprehensive Cancer Network (NCCN), [65]. Within this framework, we identified pharmacogenomic annotations related to lung cancer.

### 2.8. In silico drug prescriptions targeting therapeutic actionable genomic alterations

*In silico* drug prescription, as conducted by the CGI, is an alternative approach for identifying therapeutically actionable genomic alterations in tumors to assess their response to specific drugs [49]. This process involves ranking biomarkers based on its clinical relevance, utilizing resources like the Cancer Biomarker and Bioactivities Databases to find strong relationships between genomic

variations and drug efficacy [50,68]. In our analysis, we determined the most effective drugs for lung cancer patients by analyzing the oncogenic variome and applying precision oncology strategies.

### 2.9. Drugs in advanced clinical trial phases

The Open Targets Platform (https://www.targetvalidation.org) brings reliable integration of data, enabling the visualization of therapeutic proteins and targeted drugs associated with clinical trials [69,70]. In addition, a repository for drugs and drug-like compounds evaluated in clinical trials or approved by the US Food and Drug Administration (FDA), called the Drug Repurposing Hub (https://www.broadinstitute.org/drug-repurposing-hub), provides detailed information on their mechanisms of action, therapeutic indications, and biological activities [70,71].

## 3. Results

### 3.1. Epidemiology of lung cancer

According to the GLOBOCAN 2022, Hungary (47.6), New Caledonia (41.8), China (40.8), Serbia (40.4), French Polynesia (40.0), North Korea (38.4), Türkiye (37.9), Croatia (37.1), Montenegro (36.7), and Poland (36.5) have the highest incidence rates of lung cancer per 100,000 individuals. (Fig. 1A and Supplementary Table 1). Meanwhile, Hungary (39.8), Türkiye (35.1), French Polynesia

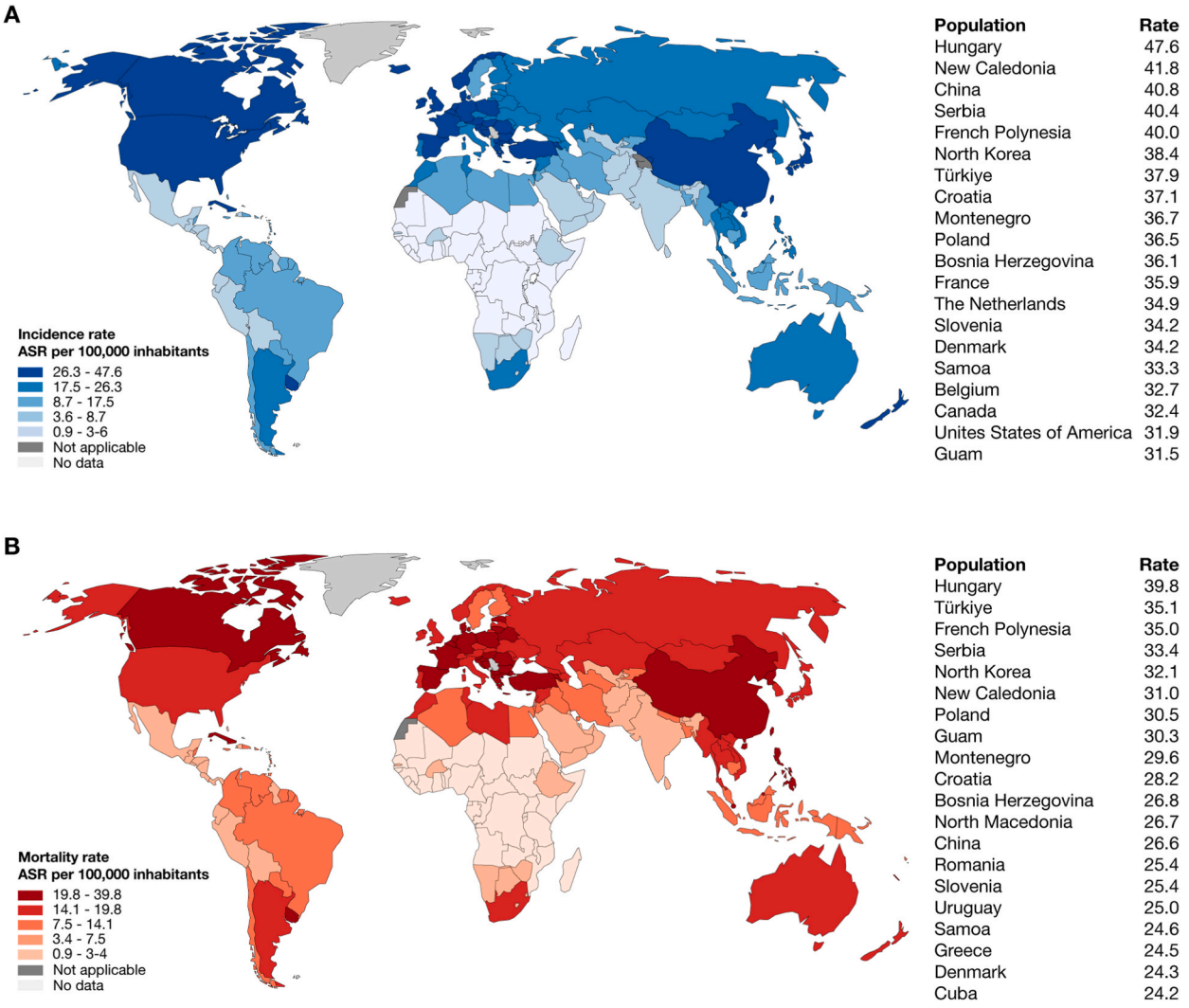


**Fig. 1.** Epidemiology of lung cancer. **(A)** Heatmap and ranking of estimated age-standardized incidence rate of lung cancer per 100,000 inhabitants worldwide. **(B)** Heatmap and ranking of estimated age-standardized mortality rate of lung cancer per 100,000 inhabitants worldwide. ASR: age-standardized rate.

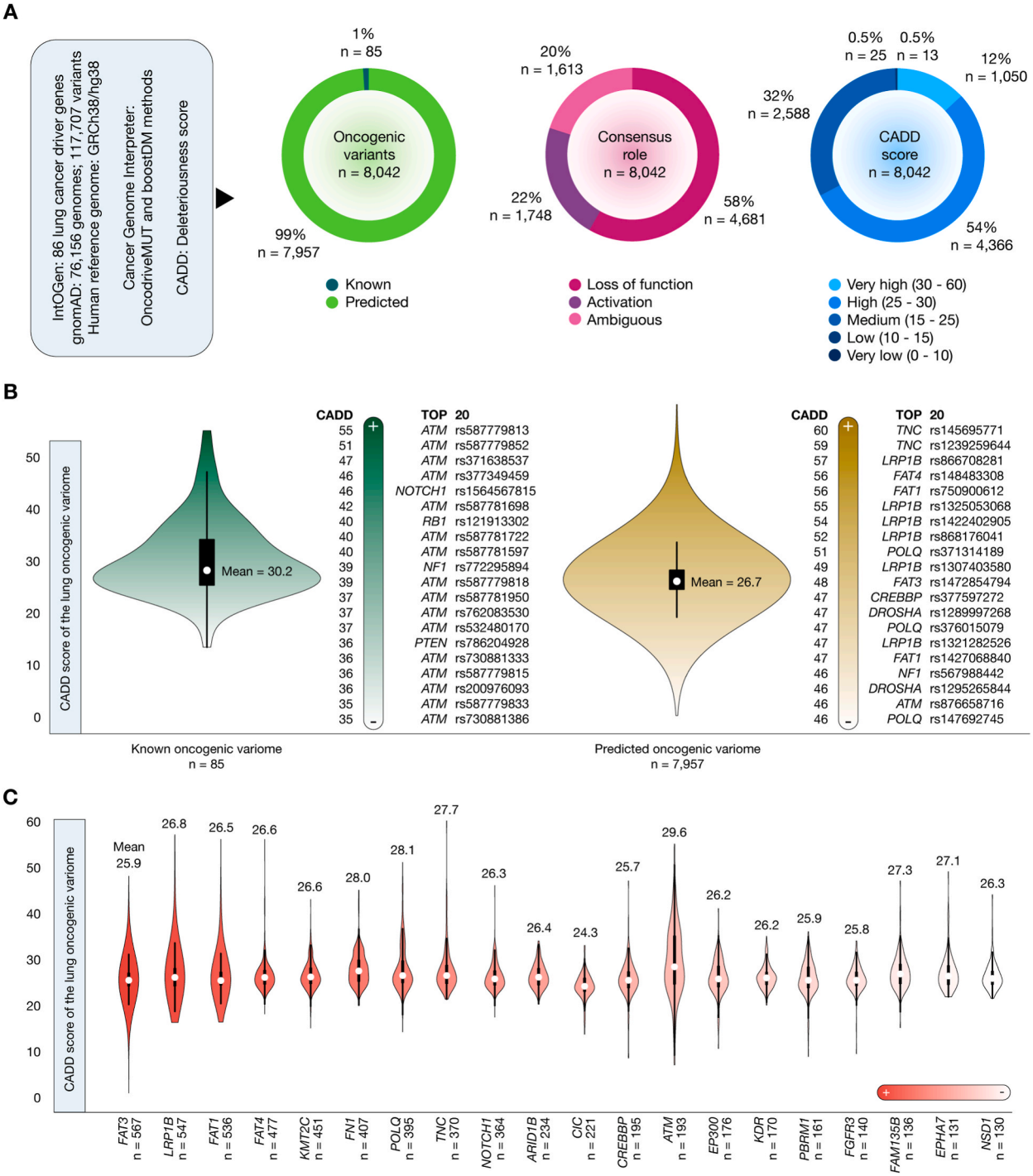


**Fig. 2.** Lung cancer driver genes, oncogenic variants, and CADD deleteriousness scores. **(A)** Features of lung cancer driver genes, oncogenic variants, consensus role and CADD deleteriousness scores. **(B)** Bean plots of CADD deleteriousness scores of the lung oncogenic variome, and ranking of known and predicted oncogenic variants with the highest CADD deleteriousness scores. **(C)** Ranking of the lung cancer driver genes with the highest number of oncogenic variants and their mean CADD deleteriousness scores.

(35.0), Serbia (33.4), North Korea (32.1), New Caledonia (31.0), Poland (30.5), Guam (30.3), Montenegro (29.6), and Croatia (28.2) have the highest mortality rates (Fig. 1B and Supplementary Table 2) [3].

### 3.2. Genes driving lung cancer

We extracted 86 lung cancer-driving genes from the intOGen platform [29]. Among these, 45 (60 %) were tumor suppressor genes [38], 39 (52 %) were metastatic genes [45], 28 (37 %) were oncogenes [38], 11 (15 %) were kinase genes [39,40], 8 (11 %) encoded RNA-binding proteins [43], 5 (7 %) were cell cycle genes [44], 3 (4 %) were cancer immunotherapy genes [46], and 2 (3 %) were DNA-repair genes [41,42] (Supplementary Table 3).

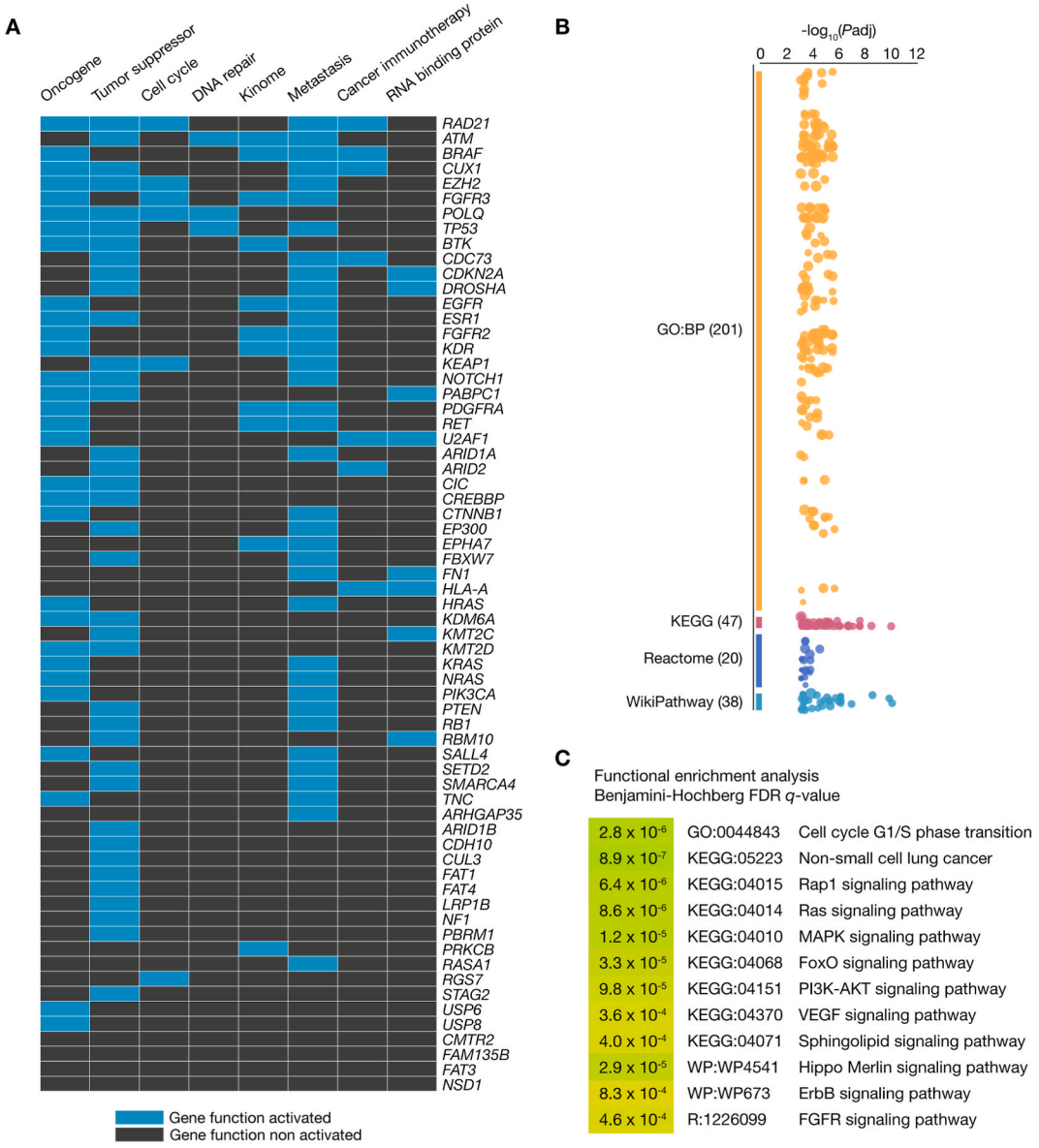


**Fig. 3.** Functional enrichment analysis. **(A)** Heatmap of lung cancer driver genes with oncogenic variants being part of oncogenes, tumor suppressor genes, cell cycle genes, DNA repair genes, kinome, metastatic genes, cancer immunotherapy genes, and genes encoding RNA-binding proteins. **(B)** Manhattan plot of the most significant GO biological processes (n = 201), KEGG signaling pathways (n = 47), Reactome signaling pathways (n = 20), and WikiPathways (n = 38). **(C)** Most relevant (Benjamini-Hochberg FDR q-value <0.001) GO biological processes, KEGG signaling pathways, Reactome signaling pathways, and WikiPathways where the lung cancer driver genes with oncogenic variants were involved.

### 3.3. Lung cancer variome deleteriousness scores

Fig. 2A depicts the data obtained from analyzing 117,707 alterations using boostDM and OncodriveMUT, focusing on the lung cancer variome across 86 driver genes. The study identified 8042 pathogenic variants, with 85 (1 %) already annotated and 7957 (99 %) predicted to be pathogenic. Most of the oncogenic variants caused loss of function (58 %) or protein activation (22 %), as

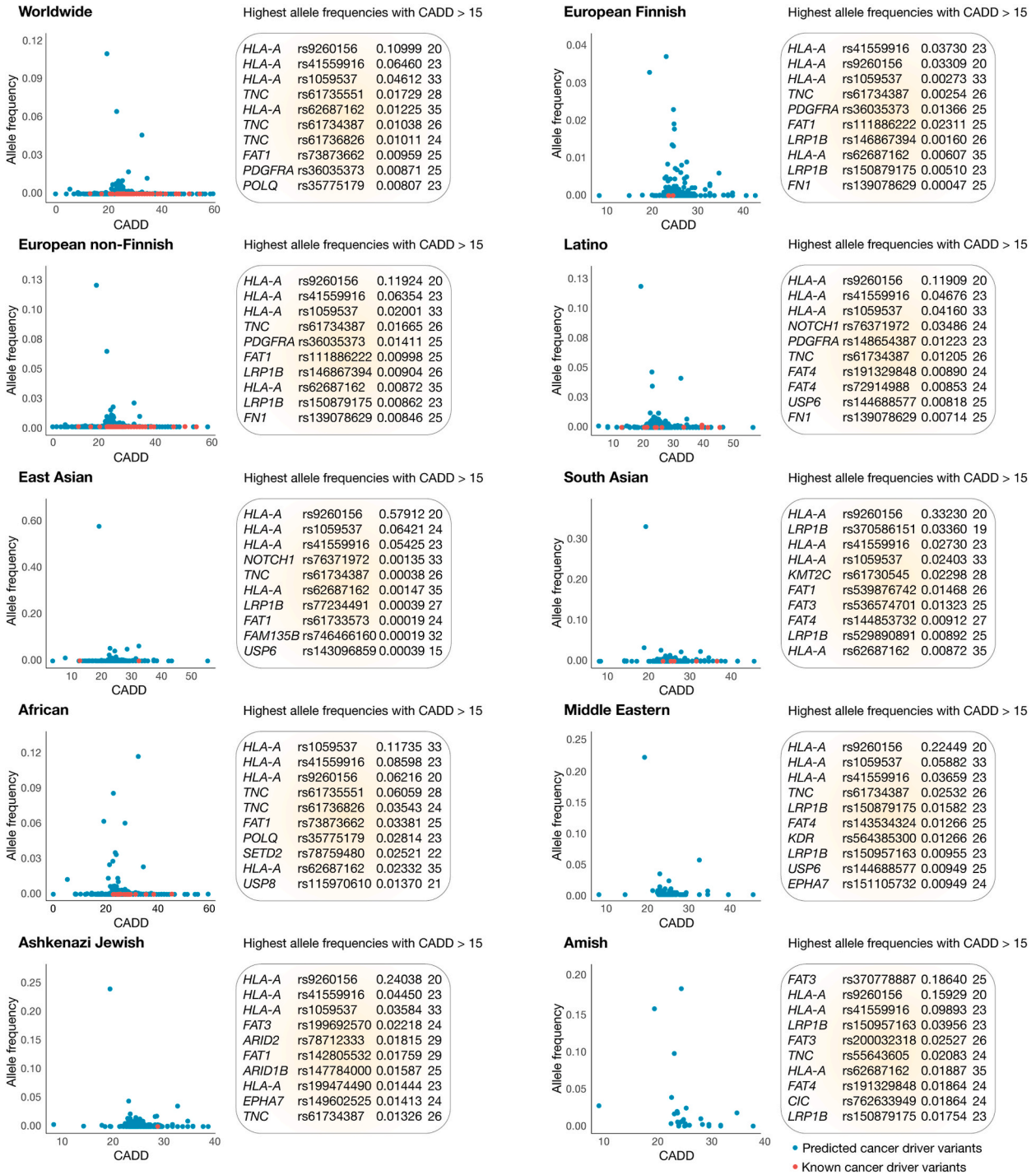


**Fig. 4.** Lung cancer oncogenic variants with the highest allele frequencies and CADD deleteriousness scores. Scatter plots and ranking of the known and predicted oncogenic variants with the highest allele frequencies and CADD deleteriousness scores (>15) from the European Finnish, European non-Finnish, Latino, East Asian, South Asian, African, Middle Eastern, Ashkenazi Jewish, and Amish populations.

determined by the consensus role. According to CADD deleteriousness scores, 1050 (12 %) of these pathogenic variants received very high scores, 4366 (54 %) had high scores, and 2588 (32 %) were assigned medium scores. The consequence type showed that most variants were missense (93 %), with the remainder being splice acceptor, splice donor, stop-gain or splice region variants. Additional details on these genomic alterations are available in Supplementary Table 4.

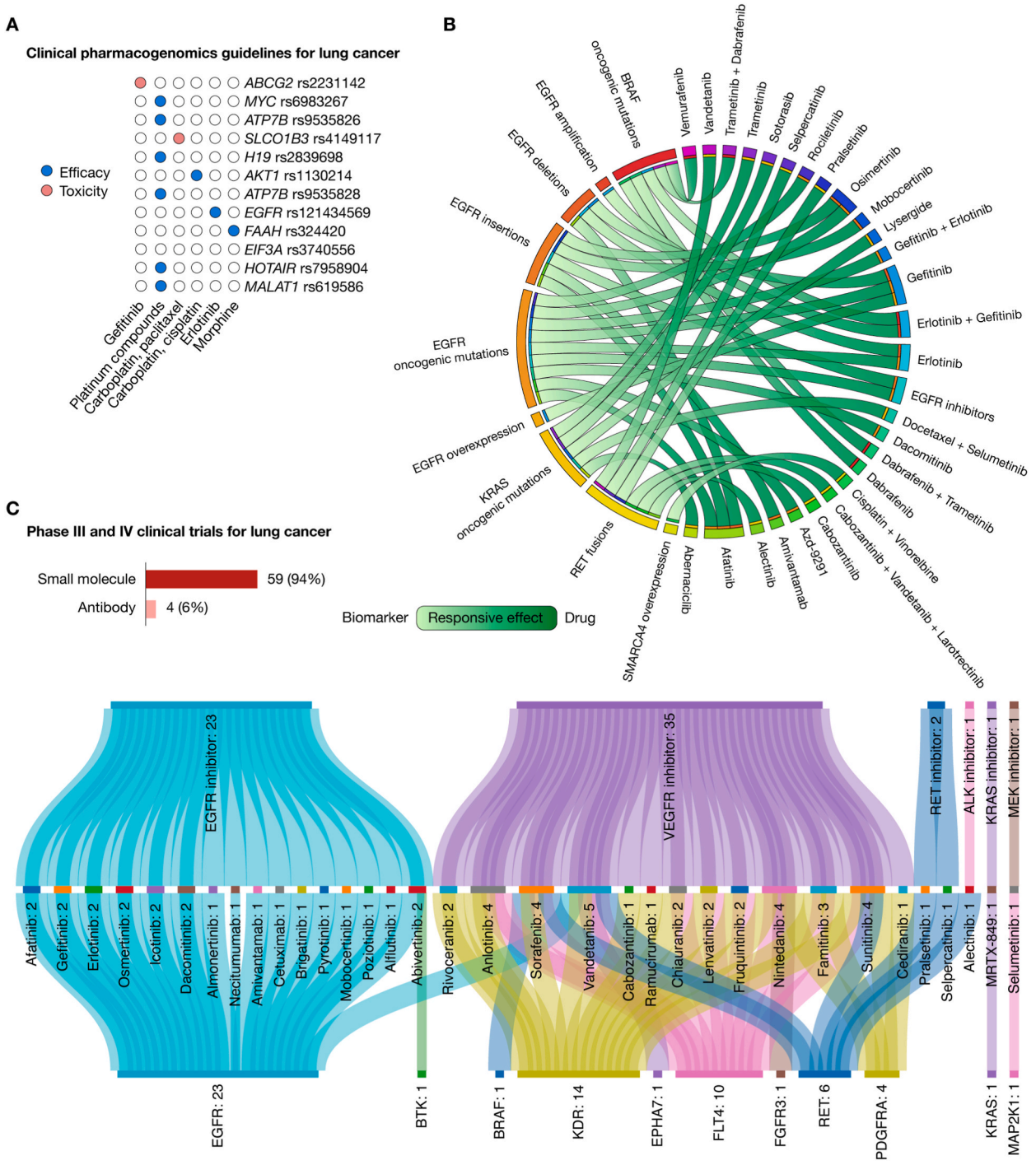


**Fig. 5.** Landscape of therapeutic strategies based on precision oncology. **(A)** Current clinical pharmacogenomic guidelines for lung cancer focused on efficacy and toxicity. **(B)** Circos plot showing *in silico* drug prescriptions of responsive effects targeting lung cancer actionable genomic alterations. **(C)** Sankey plot of phase III and IV clinical trials for lung cancer connecting therapeutic targets (n = 11), drugs (n = 34), and mechanisms of action (n = 6).

Fig. 2B visualizes violin plots and rankings of deleteriousness scores for lung cancer alterations associated with drivers. The mean CADD score for already annotated mutations was 30.2, with the highest score (n = 55) observed for *ATM* rs587779813. For predicted variants, the mean CADD score was 26.7, with the highest score (n = 60) observed for *TNC* rs145695771. The ranking of the 8042 variants is provided in Supplementary Table 5. Furthermore, Fig. 2C shows the whole amount of known and predicted lung cancer variants for each driver gene, with *FAT3* (n = 567), *LRP1B* (n = 547), and *FAT1* (n = 477) having the highest counts.

### 3.4. Functional enrichment analysis

A heatmap was generated to display the involvement of pathogenic variants in 65 genes that are implicated in lung cancer, highlighting their roles in various processes that contribute to cancer initiation and progression. Among these genes, specific groups were identified: 3 involved in DNA repair, 6 associated with the cell cycle, 7 linked to cancer immunotherapy, 8 encoding RNA-binding proteins, 11 classified as kinome genes, 30 functioning as oncogenes, 36 as metastatic genes, and 37 as tumor suppressor genes (Fig. 3A).

The enrichment analysis, visualized through a Manhattan plot, was conducted on these 65 driver genes using the entire set of cancer-associated proteins as a reference (Fig. 3B) [29,31,38]. The g:Profiler tool [57] identified numerous significant terms, including 201 biological processes from Gene Ontology (GO) [58], 47 KEGG pathways [59], 20 Reactome pathways [60], and 38 WikiPathways [61]. Noteworthy annotations with significant associations (Benjamini–Hochberg, FDR $q < 0.001$) included cell cycle G1/S phase transition (GO:0044843) and several critical signaling pathways such as Rap1 (KEGG:04015), Ras (KEGG:04014), MAPK (KEGG:04010), FoxO (KEGG:04068), PI3K-AKT (KEGG:04151), VEGF (KEGG:04370), sphingolipid (KEGG:04071), Hippo Merlin (WP:WP4541), ErbB (WP:WP673), and FGFR (R-HSA-1226099) (Fig. 3C and Supplementary Table 6).

### 3.5. Deleteriousness scores and allele frequencies across diverse ethnic backgrounds

Fig. 4 presents scatter plots that highlight both known and predicted variants exhibiting the highest allele frequencies and the most deleterious scores across various ethnic groups. The analysis categorized oncogenic variome severity into three levels based on CADD scores: medium (15–25), high (25–30), and very high (30–50). Among the groups studied, the highest average CADD score of 26.7 had the European non-Finnish, followed closely by the European Finnish (26.5), African (26.5), Latino (26.4), Ashkenazi Jewish (26.4), East Asian (26.3), South Asian (26.3), Middle Eastern (26.1), and Amish (25.8) populations.

Globally, the five alterations with the highest frequencies included *HLA-A* rs9269159 (0.10999), *HLA-A* rs41559916 (0.06460), *HLA-A* rs1059537 (0.04612), *TNC* rs61735551 (0.01729), and *HLA-A* rs62687162 (0.01225). The *HLA-A* rs9260156 variant showed the highest frequency in several populations, including European Finnish (0.03309), European non-Finnish (0.11924), Latino (0.11909), East Asian (0.57912), South Asian (0.33230), Middle Eastern (0.22449), and Ashkenazi Jewish (0.24038). In constrast, the *HLA-A* rs1059537 variant had the highest allele frequency in the African population (0.11735), and the *FAT3* rs370778887 variant was the most frequent in the Amish population (0.18640). Detailed information on allele frequencies and CADD scores for each oncogenic variant is provided in Fig. 4 and Supplementary Table 5.

### 3.6. Clinical pharmacogenomics guidelines

PharmGKB encompasses clinical guidelines and therapeutically actionable target-drug associations [62,63]. Regarding lung cancer, there are currently 12 clinical annotations involving 11 genes, 12 variants, 6 drugs, and 2 phenotype categories. Platinum compounds are effective in patients with *MYC* rs6983267, *ATP7B* rs9535826 and rs9535828, *H19* rs2839698, *HOTAIR* rs7958904, and *MALAT1* rs619686; carboplatin and cisplatin are efficient in patients with *AKT1* rs1130214 and *EIF3A* rs3740556; and erlotinib is efficient in patients with *EGFR* rs121434569. Gefitinib has toxicity in patients with *ABCG2* rs2231142; carboplatin and paclitaxel have toxicity in patients with *SLCO1B3* rs4149117; and morphine has toxicity in patients with *FAAH* rs324420 (Fig. 5A and Supplementary Table 7).

### 3.7. In silico drug prescriptions targeting therapeutic actionable genomic alterations

Putative drug response markers in lung cancer treatments obtained from the Cancer Biomarker Database are illustrated as a circos plot in Fig. 5B [68]. Individuals with *BRAF* oncogenic variants respond well with dabrafenib, vemurafenib, and combinations of dabrafenib with trametinib, erlotinib with gefitinib, and trametinib with dabrafenib. *EGFR* amplifications respond to a combination of erlotinib and gefitinib; *EGFR* deletions to afatinib, erlotinib, and gefitinib; *EGFR* insertions to afatinib, amivantamab, mobocertinib, and osimertinib; *EGFR* oncogenic mutations to afatinib, AZD-9291, dacomitinib, erlotinib, gefitinib, osimertinib, and rociletinib; EGFR overexpression to gefitinib; *KRAS* oncogenic mutations to abemaciclib, lysergide, sotorasib, trametinib, and a combination of docetaxel with selumetinib; *RET* fusions to alectinib, cabozantinib, pralsetinib, selpercatinib, vandetanib, and combinations of cabozantinib, vandetanib, and larotrectinib; and SMARCA4 overexpression to a mixture of cisplatin with vinorelbine (Supplementary Table 8).

### 3.8. Drugs in advanced clinical trial phases

The Open Targets Platform continuously provides updates on the progression of clinical trials targeting proteins implicated in lung

cancer [69,70], while the Drug Repurposing Hub outlines the function and therapeutic approaches for FDA-approved drugs [71]. Fig. 5C illustrates a Sankey diagram that represents 197 clinical trial events (95 % in phase III and 5 % in phase IV). These trials involve 11 targetable proteins (including EGFR, KDR, FLT4, RET, PDGFRA, BTK, BRAF, EPHA7, FGFR3, KRAS, and MAP2K1), 34 drugs (the majority being small molecules at 96 %, with 4 % being antibodies), and 6 distinct mechanisms of action, such as inhibitors targeting EGFR, VEGFR, RET, ALK, KRAS, and MEK. Lastly, the drugs most frequently associated with these clinical trial events were vandetanib (n = 5), anlotinib (n = 4), sorafenib (n = 4), nintedanib (n = 4), and sunitinib (n = 4) (Supplementary Table 9).

## 4. Discussion

Precision oncology represents a paradigm shift in cancer treatment, advocating for personalized therapeutic strategies. This approach meticulously considers the tumoral heterogenic microenvironment, its biological features, and various individual-specific factors such as clinical data, genetic predisposition, internal clocks, and lifestyle [72–74]. It operates on the understanding that molecular alterations in tumors are predominantly shared across multiple cancer types. As a result, the most effective cancer treatments can be tailored to each individual by analyzing the unique molecular profile of their tumor. Bioinformatics tools play a crucial role in this process, enabling the interpretation of intricate omics data, which is essential for identifying the most suitable treatment for each patient. This demonstrates the transformative potential of precision oncology in revolutionizing cancer treatment [75].

The ability to identify oncogenic variants and deliver personalized therapeutic strategies to lung cancer patients using multi-omics profiles generated through cutting-edge technologies represents a significant step towards implementing PGx in clinical practice. However, several challenges persist in implementing PGx, particularly in developing regions. These challenges include the need for established PGx clinical guidelines, cost-effectiveness studies, regulatory bodies to facilitate the use of PGx tests, and the necessity for gene-drug interaction studies [76]. Additionally, the underrepresentation of minority populations in cancer genome studies (dominated by Caucasian populations at 91.1 %) and the lack of investment in genomic testing have led to fragmented healthcare systems and a poor understanding of pharmacogenomic variability in these populations [27,77]. Therefore, in this study, we identified the most common actionable genomic alterations in the lung cancer variome, calculated their frequencies across global populations, and prioritized treatments rooted in precision oncology. This approach aims to effectively allocate resources and shape prevention strategies.

Through the analysis of 117,707 insertion/deletion and single nucleotide variants located in 86 lung cancer driver genes within 75,109 genomes from diverse ethnic populations, we identified 8042 known and predicted pathogenic variants. These included 85 previously annotated oncogenic variants, 1613 loss-of-function variants, and 1050 variants with very high deleteriousness scores. The genes with the most oncogenic variants were *FAT3*, *LRP1B*, *FAT1*, *FAT4*, *KMT2C*, *FN1*, *POLQ*, *TNC*, *NOTCH1*, and *ARID1B*. The top ten genes with the highest average deleteriousness scores were *ATM*, *POLQ*, *FN1*, *TNC*, *FAM135B*, *EPHA7*, *LRP1B*, *FAT4*, *KMT2C*, and *FAT1*. Additionally, functional enrichment analysis of the 65 genes driving lung cancer harboring pathogenic variants revealed significant associations with tumorigenic pathways, including the Rap1, Ras, MAPK, FoxO, PI3K-AKT, VEGF, sphingolipid, Hippo Merlin, ErbB, and FGFR signaling pathways.

Identifying oncogenic alterations within these diverse ethnic populations is crucial for understanding their susceptibility to lung cancer development and prioritizing potential therapeutic strategies. This understanding is essential for making informed decisions regarding economic matters, public health policies, and preventative measures worldwide. For instance, our study identified the frequency of known pathogenic lung cancer variants across different ethnic groups. We found 349 alterations in the European Finnish population, 4297 in European non-Finnish, 1232 in Latino, 778 in East Asian, 750 in South Asian, 3018 in African, 82 in Middle Eastern, 218 in Ashkenazi Jewish, and 30 in the Amish population. The most frequent pathogenic variant in the European Finnish population was *HLA-A* rs41559916 (0.03730), while in the European non-Finnish, Latino, East Asian, South Asian, Middle Eastern, and Ashkenazi Jewish populations was *HLA-A* rs9260156 (with varying frequencies of 0.11924, 0.11909, 0.57912, 0.33230, 0.22449, and 0.24038, respectively). In the African population, the *HLA-A* rs1059537 variant was the most frequent, and in the Amish population, *FAT3* rs370778887 (0.18640) was predominant. A deep understanding of these variants is critical for devising preventive strategies and tailoring effective treatment options for lung cancer patients in these populations [78,79].

An essential aim of interpreting cancer genomes is to evaluate how oncogenic variants affect the cancer treatment efficacy. By identifying the most common alterations within various populations, our research integrated these findings with current clinical pharmacogenomics guidelines [63], *in silico* drug recommendations [50], and data from late-stage clinical trials [70]. This approach enhances the identification of significant oncogenic alterations in cancer patients, facilitating the development of more tailored and effective treatment plans for lung cancer patients across diverse ethnic backgrounds.

Ten lung cancer driver genes harbor 625 known and predicted alterations with the highest frequencies and deleteriousness scores across different populations. BRAF, a serine/threonine-protein kinase involved in the MAPK/ERK signaling pathway, is linked to non-small cell lung cancer through mutations like V600E, which drive tumor growth by enhancing cell proliferation and survival [80]. EPHA7, a receptor tyrosine kinase, influences developmental processes, cell adhesion, migration, and differentiation, with altered expression implicated in lung cancer progression and metastasis [81]. FGFR3, another receptor tyrosine kinase, regulates cell growth, differentiation, and angiogenesis, with mutations promoting tumorigenesis through aberrant signaling pathways [82,83]. KDR (VEGFR2), a key receptor in the VEGF pathway, promotes angiogenesis and vascular permeability, supporting tumor growth and metastasis when overexpressed or mutated [84]. PDGFRA, a receptor tyrosine kinase, regulates cell growth and development, with mutations contributing to various cancers, including lung cancer, by stimulating uncontrolled cell proliferation [85]. RET, essential for neural crest development, influences cell survival and differentiation. *RET* fusions and mutations in NSCLC activate downstream signaling pathways, contributing to tumor growth [86]. BTK, involved in B-cell receptor signaling, impacts B-cell development and

function. BTK inhibitors, though primarily for hematological malignancies, are explored for modulating the tumor microenvironment in solid tumors, including lung cancer [87]. EGFR, crucial in regulating cell proliferation, survival, and differentiation, commonly harbors mutations in NSCLC, particularly in non-smokers, and is a target for tyrosine kinase inhibitors [88]. SMARCA4 regulates gene expression through chromatin structure alterations. Mutations in *SMARCA4* are associated with aggressive NSCLC forms, often correlating with poor prognosis and treatment response [89]. Lastly, *KRAS* transmits signals promoting cell growth and division. *KRAS* mutations are prevalent in NSCLC, especially adenocarcinomas, and are more frequent in smokers [90].

Regarding responsive treatments, Europeans of Finnish descent have 27 variants in the therapeutic targets *BRAF*, *EPHA7*, *FGFR3*, *KDR*, *PDGFRA*, and *RET*. Europeans of non-Finnish descent have 368 variants in *BRAF*, *BTK*, *EGFR*, *EPHA7*, *FGFR3*, *KDR*, *PDGFRA*, *RET*, and *SMARCA4*. Latinos have 90 variants in *BTK*, *EPHA7*, *FGFR3*, *KDR*, *KRAS*, *PDGFRA*, and *RET*. East Asians have 56 variants in *BTK*, *EPHA7*, *FGFR3*, *KDR*, *PDGFRA*, and *RET*. South Asians have 64 variants in *BTK*, *EPHA7*, *FGFR3*, *KDR*, *PDGFRA*, and *RET*. Africans have 263 variants in *BTK*, *EGFR*, *EPHA7*, *FGFR3*, *KDR*, *PDGFRA*, *RET*, and *SMARCA4*. Middle Eastern populations have 8 variants in *EPHA7*, *FGFR3*, *KDR*, *PDGFRA*, and *RET*. Ashkenazi Jewish populations have 15 variants in *EPHA7*, *FGFR3*, *KDR*, *PDGFRA*, and *RET*. And, Amish populations have 4 variants in *EPHA7*, *PDGFRA*, and *RET*. Additionally, specific drugs act on these targets. For instance, dabrafenib, trametinib, vemurafenib, and sorafenib act on BRAF [91]; abivertinib acts on BTK [92]; afatinib, amivantamab, Azd-9291, dacomitinib, erlotinib, gefitinib, mobocertinib, osimertinib, rociletinib, icotinib, almonertinib, necitumumab, cetuximab, brigatinib, vandetanib, pyrotinib, abivertinib, poziotinib, and aflutinib act on EGFR [93]; vandetanib acts on EPHA7; nintedanib acts on FGFR3; rivoceranib, anlotinib, chiauranib, rivoceranib, fruquintinib, vandetanib, lenvatinib, sorafenib, sunitinib, famitinib, nintedanib, cabozantinib, and ramucirumab act on KDR [94]; abemaciclib, docetaxel, selumetinib, lysergide, sotorasib, trametinib, and MRTX-849 act on KRAS [95]; cediranib, famitinib, sunitinib, and nintedanib act on PDGFRA [96]; alectinib, cabozantinib, vandetanib, larotrectinib, pralsetinib, selpercatinib, sunitinib, and sorafenib act on RET fusion [97]; and, cisplatin and vinorelbine act on SMARCA4 [98].

In the precision oncology era, PGx testing is crucial for optimizing resource use, enhancing patient safety, and fine-tuning drug dosage in lung cancer treatment. As genotyping technologies become more accessible, addressing inter-individual differences in drug response through PGx is becoming increasingly feasible. This represents a significant step towards integrating genomic and epigenomic medicine into mainstream healthcare [73,99–101]. However, challenges remain in implementing PGx within healthcare systems, requiring updates to clinical pathways and increased pharmacogenomic education among healthcare professionals. Expanding genetic and genomic research funding in developing countries and ensuring the inclusion of racial and ethnic minorities in clinical trials are crucial. These efforts are essential for integrating pharmacogenomics into public health policies and clinical practice, thereby improving global healthcare, especially in precision oncology [102–106].

## Consent for publication

All authors agree to publish the article on Heliyon.

## Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary material.

## CRediT authorship contribution statement

**Gabriela Echeverría-Garcés:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **María José Ramos-Medina:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Ariana González:** Writing – review & editing, Validation, Resources, Investigation, Formal analysis. **Rodrigo Vargas:** Writing – review & editing, Validation, Resources, Investigation, Data curation. **Alejandro Cabrera-Andrade:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Isaac Armendáriz-Castillo:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Jennyfer M. García-Cárdenas:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **David Ramírez-Sánchez:** Writing – review & editing, Validation, Investigation, Formal analysis. **Adriana Altamirano-Colina:** Writing – review & editing, Validation, Investigation, Formal analysis. **Paulina Echeverría-Espinoza:** Writing – review & editing, Validation, Investigation, Formal analysis. **María Paula Freire:** Writing – review & editing, Validation, Investigation, Formal analysis. **Belén Ocaña-Paredes:** Writing – review & editing, Validation, Methodology, Formal analysis. **Sebastián Rivera-Orellana:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Santiago Guerrero:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Luis A. Quiñones:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis. **Andrés López-Cortés:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## 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.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37488.

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