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# Germline pharmacogenomic predictors of treatment-related toxicity in non-small cell lung cancer: a systematic review of the discovery-to-implementation gap

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## Abstract

Background: Germline pharmacogenomic variants that predict treatment toxicity have entered routine care for a few drug-gene pairs; however, most reported associations never reach the clinic. Non-small cell lung cancer (NSCLC) isolates the problem: somatic genotyping is standard, toxicity limits dose intensity across every modality, and no germline marker guides therapy.

Methods: Following a registered protocol (PROSPERO CRD420261364865), we searched four databases for studies published between January 2020 and March 2026 and synthesized 35 studies from 15 countries. Thirty-four associations were grouped by mechanism: drug metabolism and transport (*ABCB1*, *ABCC1*, *ABCG2*, *ATIC*, *MTHFR*, *CDA*, *NRF2*, *PPARα*), DNA

repair and cell cycle (*XRCC1*, *ERCC5*, *CCND1*, *hTERT*, *TP53*/*RAD51*), immune regulation (HLA class I and II, *IL7*, *PDCD1*, *DOCK8*, *NOD2*, *STAT1*) and target pathway signaling (*GPR68*, *GRID2*, *FGF14*, *SERPINA5*, *EPO*, *KRAS*-variant); two further associations lie at non-characterized loci. The twelve strongest candidates were benchmarked against the CPIC evidence hierarchy.

Results: Thirty associations reached statistical significance; only two remained significant under a multiplicity-corrected threshold. The largest effects came from the smallest cohorts: *XRCC1* rs25487 (OR=16.33; n=52) falls to OR=2.00 at n=285 and reverses in a 486-patient radiotherapy cohort. Five of 35 studies included an independent validation cohort, and none of the benchmarked candidates reached the level required for pre-emptive testing. Across the 20 associations that reported an increased risk of toxicity together with a ratio estimate and an NSCLC-specific sample size, effect estimates scaled inversely with sample size (Spearman $\rho=-0.64$, $P=0.002$): the smaller the study, the larger the reported effect, the expected signature of the winner's curse, whereby the first published estimate of an association is inflated by the significance threshold it had to cross.

Conclusions: Although numerous germline biomarkers of treatment toxicity have been reported in NSCLC, the current evidence base remains predominantly exploratory. Independent validation is uncommon, effect-size inflation is very common, and none of the strongest candidates meet the evidentiary standards required for clinical implementation. Therefore, the principal challenge is not biomarker discovery but evidence maturation. We propose a four-phase translational framework to move NSCLC toxicity pharmacogenomics from candidate association to clinically actionable, genotype-guided care.

Keywords: genomic medicine implementation; pharmacogenomics; germline variants; treatment-related toxicity; non-small cell lung cancer; immune-related adverse events; clinical translation; winner's curse

## 1. Background

Pharmacogenomic testing has changed practice for a handful of drug-gene pairs. Pre-treatment genotyping is recommended or routine before fluoropyrimidines [1], irinotecan [2], abacavir [3] and carbamazepine [4], and for the last two, prospective screening has been shown to prevent severe hypersensitivity reactions [3,4]. Each of these drug-gene pairs completed the same implementation sequence: a candidate association, independent replication in non-overlapping cohorts, functional evidence, and prospective demonstration of clinical benefit. Most reported associations never complete that sequence, and the barriers are more often evidentiary than biological [5].

Non-small cell lung cancer (NSCLC) isolates the problem. Lung cancer is the leading cause of cancer-related mortality worldwide [6] and NSCLC accounts for approximately 85% of cases. Molecular characterization of the tumor is already routine in this disease: somatic testing for actionable alterations, including *EGFR*, *ALK*, *ROS1*, *BRAF* and *KRAS* G12C, is combined with PD-L1 immunohistochemistry to select first-line treatment [7]. Treatment-related toxicity constrains every modality and takes a different form in each: myelosuppression, nephrotoxicity and peripheral neuropathy with platinum-based chemotherapy; pneumonitis, hepatitis, colitis and endocrinopathies with immune checkpoint inhibitors; hepatotoxicity and rash with kinase inhibitors; and esophagitis with thoracic radiotherapy. Immune-related adverse events (irAEs) of any severity affect about 17% of patients receiving a PD-L1 inhibitor, 27% a PD-1 inhibitor and 54% a CTLA-4 inhibitor across cancer trials [8], and 50% of patients given first-line platinum-based chemotherapy for advanced NSCLC require a dose reduction of at least 15% [9]. The genotyping infrastructure exists and the clinical need is explicit; however, no germline variant is currently recommended for pre-treatment testing in this disease by any major pharmacogenomics guideline body [10,11].

Previous reviews have covered this ground one modality at a time: a meta-analysis of polymorphisms and platinum toxicity [12], a review of germline variation affecting targeted agents [13], and narrative reviews of single drug-gene pairs [14]. None spans all modalities or asks what each association would require to become clinically actionable. This review addresses both questions together.

This systematic review has two aims. The first is descriptive: to identify germline variants linked to treatment-related toxicity in NSCLC, to classify them by biological mechanism, and to assess study quality and independent validation. The second is translational: to benchmark the strongest candidates against the CPIC/PharmGKB evidence hierarchy and to define the steps required to reach implementation. We hypothesize that the limited clinical translation of NSCLC toxicity pharmacogenomics is explained less by biological complexity than by recurring features of the evidence-generation process itself: underpowered discovery cohorts, inconsistent endpoint definitions and the absence of independent replication. We therefore compiled the reported associations and identified where candidate biomarkers stall along the pathway from discovery to clinical adoption.

## 2. Methods

### 2.1. Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [15] and prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD420261364865). One amendment to the registered protocol was filed on the day the searches were run, extending the publication window from December 31, 2025, to March 31, 2026, before screening began (Supplementary Methods, S5).

### 2.2. Eligibility Criteria

We included studies reporting germline variants in relation to treatment-related toxicity in adults with NSCLC, under any treatment modality, graded with an objective system (Common Terminology Criteria for Adverse Events [CTCAE] versions 3-5, WHO criteria, or equivalent). Eligible articles were original publications and congress abstracts reporting complete association data, published between January 1, 2020 and March 31, 2026 in English, Spanish, Portuguese, Italian or French. We excluded narrative reviews, editorials, case reports, preclinical studies, and reports that provided neither an effect estimate nor a formal statistical test of association.

This review focused on studies published from January 2020 onwards to capture the evidence generated within the current therapeutic and genomic landscape of NSCLC. The consolidation of immune checkpoint inhibitors as standard first-line therapy, widespread molecular profiling, evolving toxicity-reporting standards, and broader use of next-generation sequencing have substantially changed the way pharmacogenomic biomarkers are evaluated. Earlier studies informed the background and benchmarking components of the review but were not included in the primary synthesis, which was intended to reflect the most relevant evidence base for contemporary clinical implementation.

### 2.3. Search Strategy

We searched PubMed/MEDLINE, the Cochrane Library, Web of Science and Embase for records published between January 1, 2020 and March 31, 2026. Both passes were run that day: the first covered the registered window (2020–2025) and the second, following the protocol amendment that extended it, covered January 1 to March 31, 2026 using identical strategies in the same four databases. Controlled vocabulary (MeSH) and free-text terms covered four concepts combined with AND: NSCLC; germline genetic variation and pharmacogenomics; treatment-related toxicity; and treatment modality or individual antineoplastic agents. The two passes returned 350 and 13 records respectively, giving 363 records before deduplication; per-

database retrievals are shown in Figure 1. Full search strings are provided in the Supplementary Material. Peer Review of Electronic Search Strategies (PRESS) was not performed.

Citation searching of the included studies and hand-searching of relevant journals yielded two further reports. One additional eligible study was identified after the database searches were closed through a targeted review of the *Journal of Thoracic Oncology* content; it is shown separately in Figure 1 and reported as such in Section 3.1.

### 2.4. Study Selection

Records retrieved from the four databases were imported into Zotero, which was used to identify and remove 69 duplicate records. Two reviewers (A.G.H. and J.O.) then independently screened the titles, abstracts, and full texts of the deduplicated set, with discrepancies reconciled by consensus; no screening-automation software was used. Inter-rater agreement was not quantified; per-reviewer decision logs were not preserved for retrospective extraction (Section 4.7).

#### 2.4.1. Definition of Independent Validation

A study was classified as having an independent validation cohort only when all four of the following criteria were met: (i) non-overlapping patient cohort; (ii) same variant or strong linkage disequilibrium (LD) proxy ($r^2 \geq 0.8$); (iii) same toxicity endpoint and CTCAE grade threshold; and (iv) directionally consistent effect ($p < 0.05$).

### 2.5. Data Extraction

First author, year, country, study design, sample size, treatment, toxicity type and grading, gene, variant identifier, effect measure (OR, HR, or RR) with 95% CI and p-value, and validation status were extracted by two reviewers (A.G.H. and J.O.). The biological mechanism was classified as drug metabolism and transport, DNA repair and cell cycle, immune regulation, target pathway signaling, or non-characterized loci for variants with no established functional annotation.

### 2.6. Quality Assessment

Two reviewers (A.G.H. and J.O.) independently assessed methodological quality using the Newcastle-Ottawa Scale (NOS) for observational studies [16], which scores selection (maximum 4 stars), comparability (2), and outcome assessment (3) for a maximum of 9. Studies were classified as high quality (NOS ≥ 7), moderate quality (NOS 5-6) or low quality (NOS ≤ 4), with discrepancies resolved by consensus.

### 2.7. Data Synthesis and Statistical Reporting

Data synthesis was qualitative and structured by biological mechanism, per the registered protocol, PRISMA 2020 guidance and the Synthesis Without Meta-analysis (SWiM) reporting guidelines [17] for narrative synthesis. Meta-analytic pooling was pre-specified only where endpoints, populations and effect-measure scales were concordant; the observed heterogeneity did not satisfy these conditions, and no pooled estimates are therefore reported. All effect sizes and p-values are reported as published; unless a study specified a multiplicity-corrected threshold, p-values were considered nominal, given that the underlying tests address heterogeneous outcomes in heterogeneous populations. No formal certainty-of-evidence assessment was applied, as the heterogeneity that precluded quantitative synthesis also precluded outcome-level grading. The conditionally pre-specified meta-analysis was consequently not performed, and this deviation from the registered protocol is reported here. The SWiM checklist is provided as Supplementary Material.

Winner's-curse-corrected estimates were derived from the published effect sizes and confidence intervals using two estimators that both condition on the significance threshold a study had to cross in order to be published, and therefore ask what true effect was most likely to have produced the estimate that was reported: conditional maximum likelihood as the primary method, and a conditional median-unbiased estimator as a sensitivity analysis (Supplementary Table S3). Conditional-likelihood corrections perform less well than empirical-Bayes and

bootstrap alternatives in genome-wide benchmarking [18], but those alternatives estimate shrinkage from the full vector of summary statistics of a single study and cannot be applied to individually selected estimates drawn from separate studies; both estimators are therefore reported. The relationship between absolute effect size and sample size was summarized by Spearman correlation with a 10,000-resample bootstrap interval.

### 2.8. Priority Variants and Benchmarking

To identify candidates for clinical translation, we designated a subset of priority variants. In contrast to the four validation criteria in Section 2.4.1, which had to be met jointly, priority status required any one of the following three criteria: independent replication or validation in the original publication, genome-wide significance, or biological plausibility through a known drug-gene pathway. Priority variants were ranked by replication status and effect size (Table 2), and their effect-allele frequencies across ancestry groups were retrieved from gnomAD v4.1 for SNPs and the Allele Frequency Net Database v3.0 for HLA alleles (Supplementary Table S2). Each priority variant was then benchmarked against the closest established CPIC/PharmGKB drug-gene precedent, and the CPIC and PharmGKB evidence levels of that precedent were recorded (Table 3); these levels describe the precedent, not the NSCLC variant.

### 2.9. Use of Artificial Intelligence

During manuscript preparation, the authors used the large language models Claude Sonnet and Claude Opus, accessed via the Biomni (Phylo) platform, to improve the language and readability of the text. Study screening, data extraction, and quality assessment were independently performed by two human reviewers (A.G.H. and J.O.), and all reported data and citations were verified against the primary publications by the authors. No generative AI tool was used to identify studies, extract or analyze data, interpret results, or generate citations

## 3. Results

### 3.1. Study Selection

The PRISMA flow diagram (Figure 1) summarizes the literature search. The database searches retrieved 363 records, 350 in the first pass and 13 in the second. After removing 69 duplicates, 294 records were screened by title and abstract and 253 were excluded because they did not address germline variants, did not report treatment-related toxicity in patients with NSCLC, or were of an ineligible publication type (narrative reviews, editorials, case reports or preclinical studies). Of the 41 reports assessed for eligibility, 8 were excluded, leaving 33 reports. Two further reports were identified by other methods, namely citation searching of the included studies and hand-searching of relevant journals, and were assessed directly for eligibility; both met the inclusion criteria, giving 35 reports. After the database searches had closed, one additional eligible study (Heersche et al., 2025) was identified through a targeted review of Journal of Thoracic Oncology content, totaling 36 reports. Two of these reports describe the same 42-patient cohort, published first as a congress abstract [45] and subsequently as a full article [46], and are counted as a single study. The qualitative synthesis therefore comprises 36 reports of 35 studies.

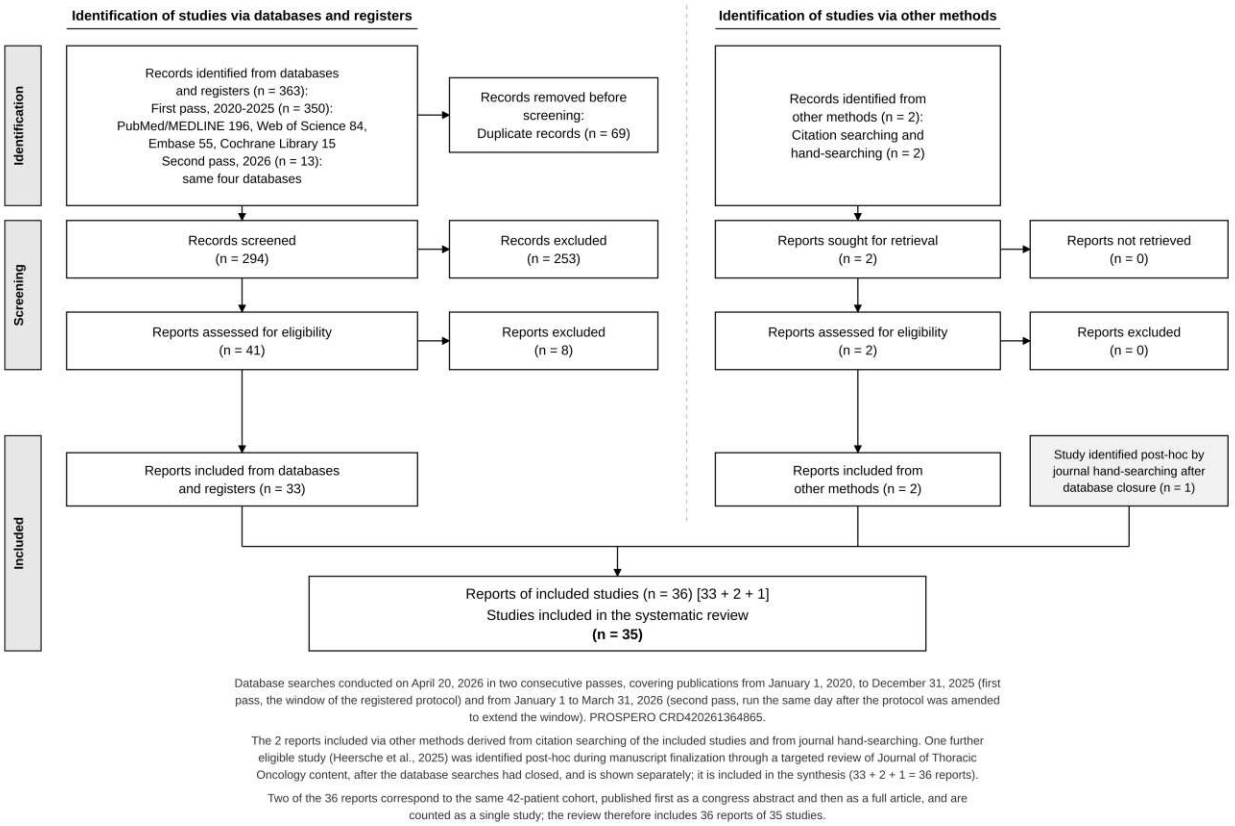



**Fig. 1 PRISMA 2020 flow diagram.** Records identified through database searching and other methods (citation searching and journal hand-searching), with reasons for exclusion at each stage. The database searches were run on April 20, 2026 in two consecutive passes, covering publications from January 1, 2020, to December 31, 2025 and from January 1 to March 31, 2026. One further eligible study was identified by journal hand-searching after the database searches had closed and is shown separately. The review includes 36 reports of 35 studies: two reports describe the same 42-patient cohort and are counted as a single study. PROSPERO CRD420261364865.

### 3.2. Study Characteristics

The 35 included studies were published between 2020 and 2026: 32 original articles (91.4%) and 3 congress abstracts (8.6%); 33 (94.3%) were cohort studies and 2 (5.7%) were case-control studies. NSCLC sample sizes ranged from 36 to 1,004 (median n=157; 34 studies reported NSCLC-specific counts). Studies originated from 15 countries across five continents. Asia was the most represented region (n=16; 45.7%). At country level, the largest contributors were China (n=8), India (n=4), and Australia, Spain and the United States (n=3 each) (Supplementary Figure S1). Treatment modalities included chemotherapy alone (n=16; 45.7%), immunotherapy alone (n=8; 22.9%), targeted therapy alone (n=3; 8.6%), and combination

regimens including chemoradiotherapy and chemoimmunotherapy (n=8; 22.9%). Five studies (14.3%) included an independent validation cohort. Detailed characteristics, including toxicity grading systems, are presented in Supplementary Table S1.

### 3.3. Quality Assessment

Newcastle-Ottawa Scale scores ranged from 5 to 9 (mean 6.5, median 7); 18 studies (51.4%) were of high quality (NOS ≥7), 17 (48.6%) were of moderate quality, and none were of low quality. Comparability was the weakest domain, with most studies scoring below the maximum available for adjusting confounders (Supplementary Figure S2).

### 3.4. Germline Genetic Associations with Treatment-Related Toxicity

Thirty-four germline associations were identified across the 35 included studies and classified into five categories based on annotated gene function rather than demonstrated causal pathways: four characterized mechanisms — drug metabolism and transport (n=9), DNA repair and cell cycle (n=5), immune regulation (n=12) and target pathway signaling (n=6) — and non-characterized loci (n=2). Thirty of these 34 associations reached statistical significance. Although 13 studies applied a correction for multiple testing (Supplementary Table S1), only two associations remained significant under a corrected threshold: *PPARα* 209G>A, which remained significant after Bonferroni correction [19], and *GRID2* rs17020773, which crossed the conventional genome-wide threshold [20]. Both are marked with an asterisk in Table 1, and *GRID2* rs17020773 is also marked in Figure 2; *PPARα* 209G>A was reported as a difference in carrier proportions rather than as a ratio estimate and therefore does not appear in the forest plot. Except where noted, p-values are quoted as published and are not corrected for the multiple variants tested within each study. The remaining four associations did not reach statistical significance; they are retained here for their biological plausibility and are explicitly labeled as non-significant trends in Sections 3.4.1 to 3.4.4 and in Table 1. Associations and their effect estimates are presented in Table 1, and the 29 variant–cohort rows are shown as a forest

plot in Figure 2. Figure 3 descriptively maps the mechanism-toxicity relationships across the mechanism categories; no formal enrichment test was performed. Mapped onto the implementation sequence, all 34 associations rest on a candidate observation, five have independent replication, none reports functional confirmation within the primary study, and none has been evaluated prospectively as a genotype-guided management strategy. Two studies fell outside the 34: one reported panel-level rather than variant-level associations [21] and the other showed no toxicity association but a survival effect [22].

**Table 1. Germline variant–toxicity associations reported by the 35 included studies (36 reports).**

| First Author, Year | Gene(s) | Variant(s) | Toxicity | Effect Measure | Effect Size (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Abed 2024 | HLA (supertypes) | HLA-A01, HLA-A03, HLA-B27 (supertypes) | irAE (any grade) | RR | HLA-A03: RR=0.35 (0.12-0.96) | p=0.066 |
| Abed 2022 | HLA-I/HLA-II | Multiple (e.g. HLA-DQB1*03:01, HLA-DRB1*0401) | irAEs | RR | HLA-DRB1*15:01: RR=0.18 (0.03-0.94); HLA-DRB1*0401: RR=1.55 (1.10-2.06) | p=0.029 / p=0.011 |
| Aguado-Barrera 2021 | Multiple (*BLM*, *FGF14*, *HSPB1*) | Multiple (e.g. *FGF14* rs4772468, *HSPB1* rs2868371) | Radiation-induced esophagitis | OR | *FGF14* rs4772468: OR=4.36 (1.15-16.46) | p=0.029 |
| Barnet 2025 | *NOD2* | LoF variants (e.g. fs1007) | irAEs (composite endpoint: clinical benefit + ≥1 grade ≥2 irAE) | Allele frequency comparison | *NOD2* LoF alleles 16.25% (13/80) vs 6.58% expected (gnomAD) | p=0.0021 (allele frequency); no variant-level test reported |
| Björn 2020 | Multiple (*DOCK8*, *SERPINA5*) | Multiple (e.g. rs34491125, rs10491684) | Thrombocytopenia | HR | *DOCK8* rs7025610: HR=2.35 (NR); *SERPINA5* rs3790036: HR=1.91 (NR) | $p=5.19\times10^{-4}$ / $p=1.47\times10^{-3}$ |
| Bushra 2020 | *XRCC1*, *GSTP1*, *XPC*, *ERCC1* | rs25487, rs1695, rs2228001, rs11615 | GI, hematologic | OR | *XRCC1* rs25487 AA+AG vs GG: OR=2.0 (1.19-3.35) | p=0.008 |
| Cafiero 2025 | Multiple (326 SNPs; *DPYD*, *UGT1A*) | 309 SNPs (e.g. *DPYD* rs12132152) | General, hematologic, GI, fatigue, cutaneous | OR | Cluster 0 + cisplatin: OR=5.25 (0.49–56.80); Cluster 1: pemetrexed OR=8.33 (0.63 - 110.03) | NR |
| Cheung 2025 [46][a] | HLA | HLA-C, HLA-DRB1*13, HLA-DPB1*02 | Pneumonitis, hepatitis, pruritus, bullous pemphigoid | p-value only | - | HLA-DPB1*02 + HLA-A*11: p=0.0032; HLA-DPB1*02 (pneumonitis): p=0.009 |
| Devika 2024 | *NRF2* | rs6721961 | Hematologic toxicity | OR | rs6721961 C>A: OR=0.46 (0.16-1.35) | p=0.159 |
| Gonzalez-Hernandez 2026 | *IL7* | rs16906115 | irAEs (general, skin, hepatic, endocrine) | OR (multivariable) | OR=4.64 (1.50-17.20) | p=0.020 |
| Guijarro-Eguinoa 2023 | Multiple (60 SNPs in 14 genes; *DPYD*) | 60 SNPs (e.g. *DPYD* c.1236G>A, c.2846A>T) | GI, hematologic, fatigue | HR (survival only) | PFS, wild type vs *DPYD* variant carriers: HR=0.057 (0.015-0.21); OS: HR=0.18 (0.06-0.50) | PFS p<0.001; OS p=0.001 |
| Heersche 2025 | *PPARα* | 209G>A* | Severe toxicity (grade ≥3) | Percentage difference | 38% vs 11% (homozygous vs WT) | p=0.004 (Bonferroni-corrected) |
| Hu 2021 | *CDA* | 435C>T | Hematologic (leucopenia) | p-value only | - | C/T vs C/C: p=0.049; C/T+T/T vs C/C: p=0.046 |
| Huang 2024 | chr3:163402331 (non-characterized locus) | rs146525069 | irAE grade ≥3 | OR (adjusted) | OR=17.08 (5.40-54.04) | $p=7.29\times10^{-8}$ |
| Huang 2022 | *LOC105373202* | rs5915369 | irAE grade ≥3 | OR (unadjusted) | OR=27.8 (3.7-206.5) | $p=6.6\times10^{-8}$ |
| Jiang 2024 | HLA | HLA-DRB4 | Endocrine irAEs | p-value; HR (PRS) | OS: HR=0.49 (0.29-0.85); PFS: HR=0.61 (0.37-1.00) | p=0.0139 (irAEs); p=0.011 (OS) |
| Kaur 2025 | *hTERT* MNS16A | VNTR MNS16A | Hematologic, nephrotoxicity, hepatotoxicity | aOR | Nephrotoxicity SS codominant: OR=0.54 (0.29-1.01) | p=0.050 |
| Khan 2023 | *GPR68*, *GRID2* | *GPR68*: rs61745750+rs61745752; *GRID2*: rs17020773* | CIPN | HR | *GPR68* (all): HR=2.44 (1.52-2.72); *GRID2* (all): HR=1.85 (1.50-2.31) | $p=1.59\times10^{-6}$ / $p=2.03\times10^{-8}$ |
| Li 2021 | *ERCC5* | rs2016073, rs4771436, rs11069498, rs4150330, rs873601 | Myelosuppression, nausea, hepatic | OR | rs11069498 allele A: OR=2.28 (1.34-3.88) | p=0.002 |
| Luo 2021 | HLA | HLA-DQA2 rs9268543 | Thyroid dysfunction | HR (PRS) | HR=1.34 (1.08-1.66) cohorts 1+2; | $p=8.73\times10^{-3}$ / p=0.010 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | (irAE) | | HR=1.39 (1.07-1.82) independent | |
| Mei 2024 | *CCND1* | rs9344 | General, GI, hematologic toxicity | OR | General tox. recessive model: OR=1.85 (1.09-3.15) | p=0.023 |
| Morau 2026 | *ABCB1* | rs2032582 | Diarrhea (any grade) | OR | non-CC vs CC: OR=7.58 (1.16-49.51) | p=0.034 |
| Polcaro 2025 | *PDCD1* (PD-1) | rs2227981, rs7421861, rs11568821, rs36084323, rs2227982, rs10204525 | irAEs | p-value only | - | rs10204525 CC: p=0.0053 (gr.1-2); p<0.0001 (gr.3-4) |
| Ritambhara/Tiwari 2022 | *XRCC1*, *XPD*, *GSTM1*, *IL1RN*, *GSTP1*, *IL1B*, *GSTT1* | Multiple (e.g. *XRCC1* rs25487) | Hematologic, GI | OR | *XRCC1* rs25487: OR=16.33 (2.66-100.26) | p=0.003 |
| Saad 2025 | *IL7* | rs7816685 (germline); rs16906062 (tumoral) | irAE (any grade) | HR (multivariable) | NSCLC rs16906062: HR=2.30 (1.16-4.60) | p=0.017 (NSCLC); interaction p=0.0012 |
| Seguin 2025 | *ABCB1*, *ABCC2* | *ABCB1* rs1045642, rs1128503, rs2032582; *ABCC2* rs717620 | Hematologic, renal, hepatic, GI | OR | *ABCB1* rs1128503 CC+CT vs TT (vomiting): OR=13.55 (1.71-107.72) | p=0.014 |
| Sharma 2023 | *ABCB1*, *ABCC1*, *ABCC2*, *ABCG2* | Multiple (e.g. *ABCB1* rs1128503, *ABCC1* rs41410450) | Hematologic, nephrotoxicity, GI, hepatotoxicity | OR, aOR | *ABCC1* rs41410450 anemia: aOR=2.70 (1.06-6.88) | p=0.030 |
| Spasic 2022 | *TP53*, *XRCC1*, *RAD51* | rs1042522 (Arg72Pro), rs25487 (Arg399Gln), rs1801320 (G135C) | General toxicity, neuropathy | OR | *TP53*/*RAD51* ArgArg/GG vs ArgArg/GC+CC: OR=0.07 (0.01-0.70) | p=0.030 |
| Takeda 2023 | Multiple (*MTHFR*, others) | Multiple (e.g. *MTHFR* rs1801133) | Hematologic and non-hematologic | OR | *MTHFR* rs1801133 CC: OR=0.13 (0.02-0.92) | p=0.040 |
| Visser 2021 | Multiple (*ATIC*, others) | Multiple (e.g. *ATIC* rs12995526) | Neutropenia, GI, fatigue | HR | *ATIC* rs12995526: HR=1.87 (1.14-3.09) | p=0.014 |
| Wang 2021 | *ABCG2*, *SLC31A1* | Multiple (e.g. *ABCG2* rs2231142, rs12505410) | Hematologic, GI | OR | *ABCG2* rs12505410 CC (neutropenia): OR=2.29 (1.28-4.10) | p=0.005 |
| Weidhaas 2023 | *KRAS* | *KRAS*-variant (3'UTR miRNA binding site) | Severe toxicity / 1-year mortality | OR | Variant vs non-variant: OR=1.18 (0.53-2.60) | p=0.690 |
| Xin 2021 | Multiple (*STAT1*, *ROS1*) | Multiple (e.g. *STAT1* rs10208033, *ROS1* rs10199181) | Hepatotoxicity | OR | *STAT1* rs10208033: OR=8.97 (1.23-65.47) | p=0.030 |
| Yang & Liu 2020 | *XRCC1*, *XRCC2*, *XPD*, *MSH2* | Multiple (e.g. *XRCC1* rs25487) | General toxicity (radiotherapy) | OR | *XRCC1* rs25487 TT: OR=0.50 (0.26-0.99) | p=0.043 |
| Zheng 2021 | *EPO* | rs1617640 | Hematologic toxicity | OR | TT vs GG+GT: OR=1.78 (1.10-2.90) | p=0.019 |

Effect sizes are shown as reported in the primary study; when several variants were tested, the estimate for the variant discussed in the text is given. *Association that remained significant after correction for multiple testing (Heersche 2025, Bonferroni; Khan 2023, genome-wide threshold). [a]Same 42-patient cohort previously reported as a congress abstract (Li 2024 [45]); the two reports are counted as one study.

CI, confidence interval; CIPN, chemotherapy-induced peripheral neuropathy; GI, gastrointestinal; irAE, immune-related adverse event; LoF, loss of function; NR, not reported; OR, odds ratio; aOR, adjusted odds ratio; OS, overall survival; PFS, progression-free survival; PRS, polygenic risk score; RR, relative risk; HR, hazard ratio; VNTR, variable number tandem repeat; WT, wild type.

### 3.4.1. Drug Metabolism and Transport

Nine associations were identified in drug transporter and metabolic enzyme genes, eight of which were statistically significant. The largest effect was for *ABCB1* rs1128503, which predicted vomiting in 110 Brazilian patients receiving paclitaxel-carboplatin (OR=13.55, 95% CI 1.71-107.72, p=0.014) [23]. In 36 Brazilian patients receiving gefitinib as targeted monotherapy, without concurrent platinum, *ABCB1* rs2032582 non-CC genotypes were associated with diarrhea (OR=7.58, 95% CI 1.16-49.51, p=0.034) [24], and *ABCC1* rs41410450 predicted anemia in 407 Indian patients receiving platinum (OR=2.70, p=0.030) [25]. *ABCG2* rs12505410 was associated with neutropenia in 1,004 Chinese patients (OR=2.29, p=0.005), discovered in 237 patients and confirmed in a replication cohort of 767 [26]. In the folate pathway, *ATIC* rs12995526 was associated with overall toxicity in 161 Dutch patients receiving pemetrexed plus platinum (HR=1.87, p=0.014) [27], and *MTHFR* rs1801133 was associated with protection against hematologic toxicity in 67 Japanese patients (OR=0.13, p=0.04) [28]. Among 163 Chinese patients receiving gemcitabine-platinum, T-allele carriers of *CDA* 435C>T developed leukopenia more often (C/T+T/T versus C/C, p=0.046; C/T versus C/C, p=0.049) [29]. *NRF2* rs6721961 showed a non-significant trend toward protection against hematologic toxicity (OR=0.46, p=0.159) [30]. In *ALK*-positive NSCLC treated with alectinib, *PPARα* 209G>A was significantly associated with grade ≥3 toxicity (38% in homozygous carriers versus 11% in wild-type, p=0.004, Bonferroni-corrected) in a Dutch multicenter cohort of 215 patients [19].

### 3.4.2. DNA Repair and Cell Cycle

Five associations were identified in DNA repair and cell cycle genes, four of which were statistically significant. *XRCC1* rs25487 (Arg399Gln) was the most frequently examined variant: it predicted hematologic toxicity in 52 Indian patients receiving carboplatin (OR=16.33, p=0.003) [31] and anemia in 285 Bangladeshi patients receiving platinum (OR=2.00, 95% CI 1.19-3.35, p=0.008) [32]. In contrast, the TT genotype was protective against severe general radiation

toxicity in 486 Chinese patients treated with radiotherapy (OR=0.50, p=0.043) [33]. *ERCC5* rs11069498 predicted overall toxicity in 506 cisplatin-treated Chinese patients (OR=2.28, p=0.002) [34], and *CCND1* rs9344 (G870A) predicted overall toxicity in 429 Chinese patients who received at least two cycles of platinum-based chemotherapy (recessive model: OR=1.85, 95% CI 1.09-3.15, p=0.023) [35]. The combined *TP53*/*RAD51* genotype was protective against overall toxicity in 121 Serbian patients (OR=0.07, p=0.03) [36], and *hTERT* VNTR MNS16A showed a non-significant trend toward protection against nephrotoxicity in 355 Indian patients (OR=0.54, p=0.05) [37].

### 3.4.3. Immune Regulation

Twelve associations were identified in immune-regulatory genes, of which 11 were statistically significant and predominantly irAEs in ICI-treated patients. *DOCK8* rs7025610 was associated with thrombocytopenia in 212 Swedish patients receiving gemcitabine/carboplatin (HR=2.35, $p=5.19\times10^{-4}$), with an independent genome-wide association study (GWAS) validation [38]. *STAT1* rs10208033 was associated with hepatotoxicity in 42 Chinese patients receiving crizotinib (OR=8.97, p=0.03) [39]. Two *IL7* variants were independently associated with irAEs: rs16906115 in 124 Spanish ICI-treated patients (OR=4.64, p=0.020) [40], and rs16906062 in a pooled analysis of 152 patients receiving pembrolizumab (HR=2.30, p=0.017), which was validated across three cohorts [41].

Among HLA alleles, HLA-DRB1*04:01 increased irAE risk in 179 Australian patients (RR=1.55, p=0.011), whereas HLA-DRB1*15:01 was protective in the same cohort (RR=0.18, p=0.029) [42]; HLA-A*03 showed a non-significant protective trend (RR=0.35, p=0.066) [43]. An HLA-based polygenic risk score was associated with ICI-induced thyroid dysfunction in a US cohort (n=729 discovery plus 561 validation; OR=1.34-1.39, p<0.01) [44]. HLA-DPB1*02 was associated with pneumonitis in a single 42-patient Hong Kong cohort, in which pneumonitis developed exclusively in HLA-DPB1*02 carriers and in no non-carrier (31.8% versus 0%,

p=0.009); in the same cohort the HLA-DPB1*02 and HLA-A*11 combination was also associated with pneumonitis (p=0.0032) [46], previously reported in abstract form [45]. In a separate 85-patient cohort, 81.8% of patients who developed endocrine irAEs carried HLA-DRB4 (p=0.0139) [47]. *PDCD1* rs10204525 C/C carriers showed higher rates of grade 1-2 and grade 3-4 irAEs across two prospective cohorts, with no grade 3-4 event in any C/T carrier [48]. Inherited *NOD2* loss-of-function variants were enriched among patients with an exceptional immune response, an endpoint that required clinical benefit together with at least one grade ≥2 irAE (13 of 80 alleles, 16.25%, versus 6.58% expected from gnomAD, p=0.0021); grade 3-4 events accounted for 31.8% of the 22 irAE events recorded in 12 carriers versus 18.8% of the 48 events in 28 non-carriers, without a reported statistical test, and the primary report describes the number and type of irAEs as similar in both groups [49].

#### 3.4.4. Target Pathway Signaling

Six associations were identified in target pathway signaling genes, of which five were statistically significant. *FGF14* rs4772468 predicted radiation-induced esophagitis in a Spanish validation cohort of 178 patients (OR=4.36, p=0.029), with confirmed independent validation [50]. A *GPR68* C-terminus missense variant, identified in a pharmacogenomic sub-study of a US trial, was associated with chemotherapy-induced peripheral neuropathy in patients receiving taxane/platinum regimens (HR=2.44, $p=1.59\times10^{-6}$) [20]. A low-frequency intronic variant in *GRID2* (rs17020773) identified in the same whole-genome sequencing cohort reached genome-wide significance for time-to-onset of chemotherapy-induced peripheral neuropathy in patients receiving taxane- or platinum-based regimens (HR=1.85, 95% CI 1.50-2.31, $p=2.03\times10^{-8}$), with a stronger signal in the taxane-treated subgroup (HR=1.96, 95% CI 1.56-2.47, $p=6.36\times10^{-9}$) [20]. *SERPINA5* rs3790036 was associated with thrombocytopenia (HR=1.91, $p=1.47\times10^{-3}$) in the same 212-patient Swedish cohort in which *DOCK8* rs7025610 was identified (Section 3.4.3), also with independent GWAS validation [38]; no confidence interval was reported for either

variant, which is why both appear without whiskers in Figure 2. *EPO* rs1617640 predicted hematologic toxicity in 437 Chinese patients receiving platinum plus gemcitabine (OR=1.78, p=0.019) [51]. In contrast, the inherited *KRAS*-variant was not significantly associated with severe toxicity or one-year mortality in the RTOG 0617 sub-study (OR=1.18, p=0.69) [52].

#### 3.4.5. Non-Characterized Loci

We identified two associations at non-characterized loci in Singaporean ICI-treated cohorts, both of which approached but did not cross the conventional genome-wide threshold: chromosome 3:163402331 rs146525069 was associated with grade ≥3 irAEs in 188 patients (OR=17.08, $p=7.29\times10^{-8}$) [53], and *LOC105373202* rs5915369 with grade ≥3 irAEs in a separate cohort of 111 patients (OR=27.8, $p=6.60\times10^{-8}$) [54]. Neither of these has been independently replicated.

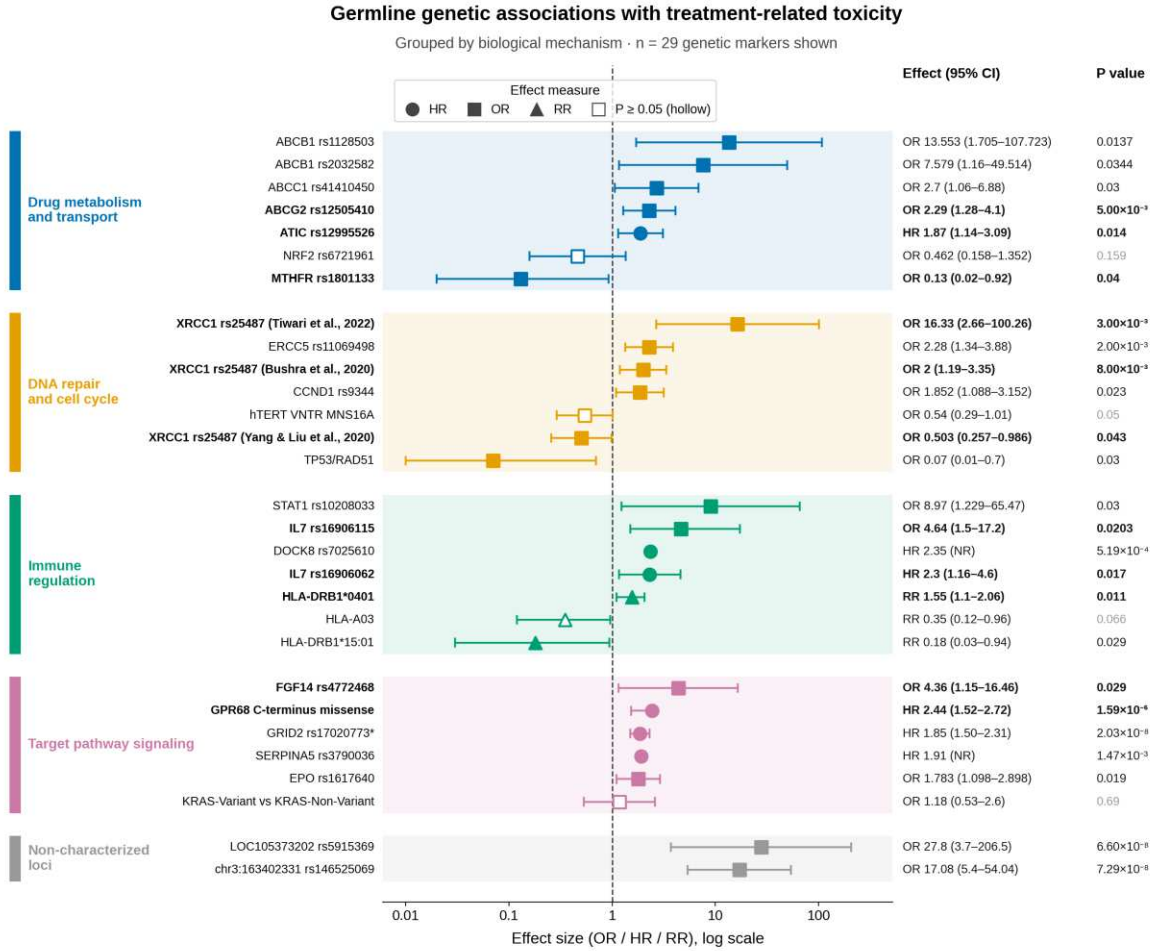



**Fig. 2 Germline variant-toxicity associations grouped by biological mechanism.** Forest plot of the 29 variant-cohort associations that report a ratio effect estimate, grouped by biological mechanism category. Each row is one variant-cohort estimate; *XRCC1* rs25487 appears in three cohorts. Associations reported without a ratio estimate for the toxicity endpoint (only p-values or carrier proportions) and the HLA polygenic risk score are not shown. Point estimates are shown with 95% confidence intervals, and the vertical line indicates the null (ratio = 1). All markers are drawn at the same size; marker area does not encode sample size. Marker shape denotes the effect measure (circle, hazard ratio; square, odds ratio; triangle, relative risk), and hollow markers denote associations with P ≥ 0.05. Associations are color-coded by mechanism: drug metabolism and transport, DNA repair and cell cycle, immune regulation, target pathway signaling, and non-characterized loci. Two markers (*DOCK8* rs7025610 and *SERPINA5* rs3790036) are shown without whiskers because no confidence interval was reported. Variant labels in bold are the priority variants of Table 2 that have a ratio estimate (eleven rows; HLA-DPB1*02, *PDCD1* rs10204525 and *PPARα* 209G>A were reported without one). An asterisk marks the single association that remained significant after correction for multiple testing (*GRID2* rs17020773).




**Fig. 3 Treatment modality, biological mechanism and toxicity phenotype across the 34 germline associations.** Sankey diagram linking treatment modality (left) to biological mechanism (center) and toxicity phenotype (right). Flow width is proportional to the number of variant-outcome associations extracted from Table 1. The number of associations assigned to each mechanism is shown next to the node label, and the genes listed beneath each node are those contributing associations to that category. *XRCC1* rs25487 and HLA-DPB1*02 are each represented by a single flow, because the three *XRCC1* cohorts share the same treatment-to-toxicity path and the two HLA-DPB1*02 reports describe the same study. The diagram is descriptive; no formal enrichment test was performed.

### 3.5. Priority Variants and Benchmarking Against the CPIC/PharmGKB Hierarchy

Twelve variants that met the priority criteria are listed in Table 2, ranked by replication status and effect size, and annotated with cross-ancestry allele frequencies. Benchmarked against the closest established CPIC/PharmGKB drug-gene precedent (Table 3), none of the 12 reached PharmGKB level 2A or above, and no CPIC level has been assigned to any of these variant-drug pairs in the NSCLC setting; *MTHFR* is the only gene among them with a CPIC assignment at all, and that assignment is level C for methotrexate, a level that carries no prescribing action. Three came closest: *ABCG2* rs12505410, resting on the largest cohort with an internal replication arm [26]; *XRCC1* rs25487, the only variant examined in three independent cohorts, though its direction of effect differs by modality [31-33]; and the *GPR68* coding variants, which

reached suggestive genome-wide significance for peripheral neuropathy ($p=1.59\times10^{-6}$) [20]. The *IL7* variants and HLA class II alleles formed a second tier of convergent but unreplicated evidence [40-42,45-47]. *GRID2* rs17020773 met the significance criterion but was not carried forward as a priority variant for three reasons: its source study reported no NSCLC-specific sample size, the variant has not been externally replicated, and it carries no functional characterization. The *GPR68* coding variants identified in the same cohort truncate the receptor C-terminus and disrupt its three arrestin-binding motifs, and their expression was localized to sensory neurons by single-nucleus RNA-sequencing of human dorsal root ganglia, whereas *GRID2* rs17020773 is a low-frequency intronic variant for which no functional consequence has been reported [20]. This benchmarking has two caveats: the remaining 22 associations were not graded, and the 2020-2026 search window excludes earlier replication and functional work that CPIC curation would weigh.

## Table 2. Twelve priority candidate variants for clinical translation in NSCLC pharmacogenomics, ranked by replication status and effect size, with cross-ancestry allele frequencies.

*Variants selected from the 34 germline associations identified in this review. Selection criteria: (i) independent replication or validation in original publication; (ii) suggestive genome-wide significance ($p<5\times10^{-6}$); (iii) biological plausibility through known drug-gene pathway. Effect-allele frequencies are reported on the study-publication strand; population data from gnomAD v4.1 (SNPs) and AFND v3.0 (HLA, sample-size-weighted).*

| Gene | Variant | Toxicity / treatment | Effect size | Study cohort (n; ancestry) | NFE | EAS | SAS | AFR | AMR | Rationale for clinical translation priority |
|---|---|---|---|---|---|---|---|---|---|---|
| ***XRCC1*** | rs25487 | Hematologic | OR=16.33 / 2.00 / 0.50 | Tiwari 2022 (India) / Bushra 2020 (Bangladesh) / Yang and Liu (China) | 0.362 | 0.259 | 0.353 | 0.143 | 0.270 | Replication across two independent South Asian studies (Tiwari 2022 [India] n=52; Bushra 2020 [Bangladesh] n=285) plus a third Chinese RT study (Yang & Liu 2020 n=486); cross-study direction is mixed (risk in chemo, protective in RT) but the largest effect size is for hematologic toxicity. Cross-study heterogeneity warrants direction-of-effect resolution |
| ***ABCG2*** | rs12505410 | Neutropenia | OR=2.29 | Wang 2021 (China) | 0.371 | 0.312 | 0.291 | 0.140 | 0.396 | Largest single cohort, with internal replication arm (Wang 2021, n=1004); two-stage discovery+replication GWAS design; G allele frequency ~30% across most superpopulations enables broad applicability |
| ***GPR68*** | rs61745750 (in rs61745750+rs 61745752 (rare coding)) | CIPN | HR=2.44 | Khan 2023 (US) | 8.96e-04 | 0.000 | 0.000 | 1.66e-04 | 3.42e-05 | Suggestive genome-wide significance ($p=1.6\times10^{-6}$); rare coding variant in compound heterozygous configuration with rs61745752 (in cis); paclitaxel-CIPN with biological plausibility (proton-sensing GPCR); extremely rare → drug-development opportunity |
| ***IL7*** | rs16906115 | irAEs | OR=4.64 | González-Hernández 2026 (Spain) | 0.084 | 0.293 | 0.094 | 0.339 | 0.169 | Independent Spanish NSCLC ICI cohort (González-Hernández 2026); concordant with US-Korean *IL7* finding (Saad 2025); irAE phenotype across two distinct cohorts and ethnicities |
| ***IL7*** | rs16906062 | irAEs | HR=2.30 | Saad 2025 (US/Korea) | 0.064 | 0.281 | 0.048 | 0.139 | 0.181 | Validated (Saad 2025) in multi-ethnic US/Korean cohort; same IL-7 pathway as rs16906115; potential mechanism via T-cell homeostasis |
| **HLA-DPB1** | *02 | Pneumonitis | (carriership) | Cheung 2025 (China) | 0.137 | 0.190 | 0.219 | 0.125 | 0.088 | Single 42-patient Hong Kong cohort reported twice (congress abstract Li 2024, then full article Cheung 2025), not independently replicated; pneumonitis phenotype with anti-PD-1/EGFR-TKI; striking EAS-NFE frequency gradient (19% vs 14%) suggests population-specific risk pattern |
| **HLA-DRB1** | *04:01 | irAE risk | RR=1.55 | Abed 2022 (Australia) | 0.074 | 0.011 | 0.014 | 0.032 | 0.021 | Australian ICI cohort (Abed 2022, n=179); biologically plausible (shared epitope; autoimmune disease association); HLA-mediated irAE risk; near-absent in East Asians (1.1%) flags non-generalizability |
| ***FGF14*** | rs4772468 | RT esophagitis | OR=4.36 | Aguado-Barrera 2021 (Spain) | 0.149 | 0.279 | 0.237 | 0.280 | 0.231 | Validated discovery+replication (Aguado-Barrera 2021); radiotherapy esophagitis phenotype; first *FGF14* NSCLC-RT toxicity association |
| ***PDCD1*** | rs10204525 | irAEs | (CC vs CT) | Polcaro 2025 (Italy) | 0.898 | 0.246 | 0.797 | 0.658 | 0.607 | Two cohorts (Polcaro 2025 Italy with replicated mechanism); miR-4717-3p-regulated PD-1 3'UTR variant; striking EAS allele frequency (~75% C/C) suggests ancestry-specific risk profile |
| ***ATIC*** | rs12995526 | Pemetrexed tox | HR=1.87 | Visser 2021 (Netherlands) | 0.466 | 0.281 | 0.321 | 0.717 | 0.372 | Drug-specific (pemetrexed-fluorouracil pathway); biologically plausible (folate metabolism, AICAR transformylase); validated cohort (Visser 2021, n=161) |
| ***MTHFR*** | rs1801133 (C677T) | Hematologic tox / pemetrexed–platinum | OR=0.13 | Takeda 2023 (n=67; Japanese) | 0.337 | 0.348 | 0.149 | 0.109 | 0.478 | Benchmarked against the highest-level precedent in this review (PharmGKB 2A, non-NSCLC); biologically plausible through altered folate pools; single small cohort, no replication |
| ***PPARα*** | rs1800206 (209G>A, L162V) | Grade ≥3 toxicity / alectinib | 38% vs 11% (p=0.004) | Heersche 2025 (n=215; Dutch) | 0.066 | 0.000 | NR | NR | NR | Only association in this review to remain significant after Bonferroni correction; concordant pharmacokinetics (+18.5% trough levels in severe toxicity); biologically plausible through PPARα-mediated regulation of CYP3A4; single cohort, no replication |

**Abbreviations:** AFND = Allele Frequency Net Database; AFR = African; AMR = admixed American (Latino); CIPN = chemotherapy-induced peripheral neuropathy; EAS = East Asian; gnomAD = Genome Aggregation Database; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; MAF = minor allele frequency; NFE = non-Finnish European; NSCLC = non-small cell lung cancer; RT = radiotherapy; SAS = South Asian. Effect-allele frequencies for genes on the minus strand have been reoriented to the publication strand and validated against published European reference frequencies. Full strand-orientation metadata are in Supplementary Table S1.

414 **Table 3. Evidence-level comparison of priority NSCLC pharmacogenomic markers against PharmGKB and CPIC evidence hierarchies**

| NSCLC variant (gene, rsID/allele) | Toxicity context | NSCLC evidence in this review | Closest established drug–gene precedent | Evidence level of the precedent | Required next step |
|---|---|---|---|---|---|
| *XRCC1* rs25487 (Arg399Gln) | Platinum hematologic toxicity; inverse direction for radiation esophagitis | 3 studies, total n=823. OR=16.33 (Tiwari 2022, n=52); OR=2.00 (Bushra 2020, n=285); OR=0.50, inverse (Yang and Liu, n=486) | No direct precedent; closest is *DPYD*–fluoropyrimidine | No CPIC level assigned; PharmGKB level 3 | Resolve direction of effect with a pre-specified, treatment-stratified analysis; replicate the hematologic association in non-Asian platinum cohorts of ≥500 patients |
| *ABCG2* rs12505410 | Platinum-induced neutropenia | 1 multicentre study, n=1,004 (Wang 2021); OR=2.29, 95% CI 1.28-4.10, p=0.005; discovery n=237, internal replication n=767 | *DPYD*-fluoropyrimidine (drug-handling gene) | CPIC level A; PharmGKB level 1A | Independent prospective replication outside Han Chinese populations; functional validation of *ABCG2* transporter activity |
| *GPR68* rs61745750 + rs61745752 (coding) | Chemotherapy-induced peripheral neuropathy | 1 clinical-trial pharmacogenomic sub-study (Khan 2023); HR=2.44, 95% CI 1.52-2.72, p=1.59×10$^{-6}$ | No direct precedent (novel neuropathy locus) | No CPIC level assigned; PharmGKB level 4 | Independent NSCLC taxane/platinum cohort of ≥500 patients; iPSC-derived sensory neuron functional studies |
| *IL7* rs16906115 + rs16906062 | All-cause immune-related adverse events | 2 independent studies. OR=4.64, 95% CI 1.50-17.20 (González-Hernández 2026, n=124, Spain); HR=2.3, 95% CI 1.16-4.6 (Saad 2025, n=152, validated across three cohorts) | Not directly analogous (cytokine pathway) | No CPIC level assigned; PharmGKB level 3 | Multi-ethnic prospective ICI cohort validation; reporter-assay confirmation of the variant effect on *IL7* transcription in T cells |
| HLA-DPB1*02 | ICI-induced pneumonitis | 1 Chinese cohort of 42 patients reported in two publications (Li 2024 [45]; Cheung 2025 [46]). Pneumonitis confined to carriers: 32% versus 0%, p=0.009; HLA-DPB1*02 + HLA-A*11, p=0.0032 | HLA-B*57:01 – abacavir hypersensitivity | CPIC level A; PharmGKB level 1A | Replication in non-Asian populations; prospective evaluation of enhanced monitoring in carriers |
| HLA-DRB1*04:01 | All-cause irAEs (with HLA-DRB1*15:01 protective in the same cohort) | 1 Australian cohort, n=179 (Abed 2022); RR=1.55, 95% CI 1.10-2.06, p=0.011 | HLA-B*15:02 – carbamazepine SJS in Han Chinese | CPIC level A; PharmGKB level 1A | Replication in independent multi-ethnic cohorts; mechanistic study of class II peptide presentation |
| *FGF14* rs4772468 | Acute radiation esophagitis | 1 validation cohort, n=178 (Aguado-Barrera 2021); OR=4.36, 95% CI 1.15-16.46, p=0.029; validates an earlier report (Pu 2014) | No direct precedent (novel radiotherapy-toxicity locus) | No CPIC level assigned; PharmGKB level 3 | Multicentre replication in concurrent chemoradiotherapy cohorts; integration into prospective radiotherapy planning protocols |
| *PDCD1* rs10204525 | Immune-related adverse events | 2 prospective cohorts (Polcaro 2025); C/C carriers with higher grade 1-2 (p=0.0053; p=0.0012) and grade 3-4 irAEs (p<0.0001; p=0.0116); no grade 3-4 event in any C/T carrier | Not directly analogous (target-gene regulatory variant) | No CPIC level assigned; PharmGKB level 3 | Multi-ethnic replication; in vitro confirmation of allele-specific miR-4717-3p binding and PD-1 expression |
| *ATIC* rs12995526 | Pemetrexed-associated overall toxicity | 1 Dutch prospective cohort, n=161 (Visser 2021); HR=1.87, 95% CI 1.14-3.09, | *TPMT*-thiopurines (antimetabolite biosynthesis) | CPIC level A; PharmGKB level 1A | Prospective replication in pemetrexed-treated NSCLC cohorts |

| | | | | | |
|---|---|---|---|---|---|
| | | p=0.014 | | | |
| *MTHFR* rs1801133 (C677T) | Hematologic toxicity, pemetrexed (protective direction) | 1 Japanese prospective cohort, n=67 (Takeda 2023); OR=0.13, 95% CI 0.02-0.92, p=0.04 | *MTHFR*–methotrexate (extensively studied outside NSCLC) | CPIC level C (no prescribing action recommended); PharmGKB level 2A (methotrexate, non-NSCLC indication) | NSCLC-specific prospective validation in an adequately powered pemetrexed cohort |
| *PPARα* 209G>A (rs1800206, L162V) | Grade ≥3 toxicity, alectinib (*ALK*-positive NSCLC) | 1 Dutch multicentre cohort, n=215 (Heersche 2025). Grade ≥3 toxicity in 38% of homozygous carriers versus 11% of patients with ≥1 wild-type allele (p=0.004), significant after Bonferroni correction; concordant pharmacokinetics (+18.5% trough levels in patients with severe toxicity). No independent replication. | *CYP3A5* before tacrolimus (CYP3A-mediated exposure) | CPIC level A; PharmGKB level 1A | Independent replication in an *ALK*-positive cohort, then a prospective test of whether dose reduction in carriers lowers grade ≥3 toxicity without compromising efficacy |

Each priority variant from Table 2 is benchmarked against the closest established drug–gene precedent. The two evidence scales are distinct and are reported separately: PharmGKB grades variant–drug annotations from level 1A (highest) through 1B, 2A, 2B and 3 to level 4 (lowest), whereas CPIC assigns gene–drug pairs to levels A through D, of which only levels A and B carry prescribing recommendations. Levels in this table describe the precedent, not the NSCLC variant: none of the benchmarked NSCLC variants reaches PharmGKB level 2A or above, and none of the benchmarked variant–drug pairs in the NSCLC setting has been assigned a CPIC level. *MTHFR* is the only gene in this table with a CPIC assignment for a different drug (level C for methotrexate, which carries no prescribing action).

CIs were omitted where the primary study reported carriership proportions rather than a ratio estimate. CI, confidence interval; CPIC, Clinical Pharmacogenetics Implementation Consortium; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; iPSC, induced pluripotent stem cell; OR, odds ratio; PharmGKB, Pharmacogenomics Knowledgebase; SJS, Stevens-Johnson syndrome.

### 3.6. Small-Study Effects and Effect-Size Inflation

Two features of the evidence base indicate that published effect sizes over-represent true magnitudes. First, every single-study genome-wide signal is positive in direction. Second, reported magnitude decreases as cohort size increases: the two Singaporean immunotherapy top hits (OR=17.08, n=188 [53]; OR=27.8, n=111 [54]) exceeded anything reported from cohorts of 200 patients or more by an order of magnitude. Twenty-seven associations reported both a ratio estimate and an NSCLC-specific sample size and are plotted in Supplementary Figure S3; across the 20 of these that describe an increased risk of toxicity, the effect size decreased as the sample size increased (Spearman ρ=-0.64, P=0.002; bootstrap 95% CI -0.83 to -0.29 over 10,000 resamples). The seven protective associations were analyzed separately because their effect estimates lie on the opposite side of the null. Formal publication-bias testing was not applicable, since no marker–outcome combination reached the ten independent studies below which tests for funnel-plot asymmetry are not recommended [55], and effect measures and outcome definitions were heterogeneous [56].

*XRCC1* rs25487 is the clearest single illustration (Supplementary Figure S4): OR=16.33 at n=52 [31], OR=2.00 at n=285 [32], and OR=0.50 for general radiation toxicity at n=486 [33].

Applied to the nine cohort-level ratio estimates for the priority variants, conditional maximum-likelihood correction [57,58] removed a median of 66% of the excess effect, and the more conservative median-unbiased estimator removed 51% (Supplementary Table S3). Even on the conservative estimator, seven of the nine corrected estimates fell below 2.0, and *IL7* rs16906115 fell from 4.64 to at most 2.41.

## 4. Discussion

We identified 34 germline associations across 35 studies published between 2020 and 2026, spanning four characterized biological mechanisms and two loci with no established functional

annotations. Candidate variants are also abundant. None have completed the implementation sequence that converts other drug-gene pairs into clinical tests. Therefore, this review contributes to the diagnosis of why the catalogue has not been translated and a specification of what would change that.

### 4.1. Drug Metabolism and Transport Variants

*ABCB1* and *ABCG2* variants predict chemotherapy toxicity, consistent with their roles as ATP-binding cassette transporters that regulate intracellular drug concentrations [59]: reduced efflux capacity may increase intracellular accumulation and amplify toxicity. *ABCG2* rs12505410 is the best supported finding in this category, discovered in 237 patients and then confirmed in an internal split-sample replication arm of 767 within the same cohort [26], whereas the *ABCB1* rs1128503 effect is striking but imprecise: the confidence interval spans a 63-fold range (OR=13.55, 95% CI 1.71-107.72) in a cohort of 110 patients, and the finding has not been replicated [23]. The *ATIC* association is biologically coherent, since *ATIC* encodes an enzyme in de novo purine synthesis that is directly inhibited by pemetrexed polyglutamates [27]. The *MTHFR* protective association is plausible through altered folate pools, though its small sample size and borderline p-value require caution [28].

*CDA* 435C>T illustrates a recurring principle: associations are most detectable when analyses are restricted to patients receiving the drug that must be metabolized by the implicated enzyme [60]. *DPYD* variants were not associated with platinum toxicity but were associated with shorter progression-free and overall survival, suggesting an effect through resistance rather than toxicity [22]. None of these has advanced beyond the first step of the implementation sequence. The *PPARα* 209G>A association with alectinib toxicity [19] extends the same principle to ALK-targeted therapy. Alectinib is cleared mainly by CYP3A4, and PPARα is a transcriptional regulator of CYP3A4 expression; a variant that alters PPARα activity could therefore alter alectinib clearance and, in turn, systemic drug exposure. This is one of the two associations

confirmed as significant after correction for multiple testing (Section 3.4), and for which the pharmacokinetic evidence is concordant: patients with severe toxicity had higher alectinib trough concentrations, that is, the plasma concentration measured immediately before the next scheduled dose. *PPARα* 209G>A is therefore the only association in this review that both survives a correction for multiple testing and is supported by concordant pharmacokinetic data. The other association that survives correction, *GRID2* rs17020773, has no accompanying pharmacokinetic evidence, and the remaining 32 rest on a nominal p-value alone.

### 4.2. DNA Repair and Cell Cycle Variants

*XRCC1* rs25487 was the most frequently replicated association in this review. Two independent studies, one in Indian [31] and the other in Bangladeshi [32] populations, reported platinum-related hematologic toxicity in the same direction, despite markedly different effect sizes (OR=16.33 versus 2.00). *XRCC1* encodes a scaffold protein essential for base excision and single-strand break repair [61]; the Arg399Gln substitution disrupts this scaffold, impairing repair at platinum-induced lesions [14]. In the radiotherapy setting the same allele acts in the opposite direction: homozygotes for the 399Gln allele, reported as the TT genotype in that study and equivalent to AA on the opposite strand, had lower odds of severe radiation-induced toxicity in 486 Chinese patients (OR=0.50, 95% CI 0.26-0.99) [33]. Three further associations in this category rest on single cohorts: *ERCC5* rs11069498 with hematologic toxicity [34], *CCND1* rs9344 [35], and the *hTERT* MNS16A VNTR, reported as protective on a nominal p-value alone. In addition, the *TP53*/*RAD51* protective association requires caution: an extreme effect size, a small sample, and a combined-genotype endpoint raise the possibility of a false positive or sparse-data bias [36]. *XRCC1* illustrates why replication alone is insufficient. The two platinum-treated cohorts agree in direction but differ eight-fold in magnitude (OR=16.33 versus 2.00), while the radiotherapy cohort reports the opposite direction under a different treatment modality. No pre-specified validation study has been performed for this variant, and only such a study,

restricted to a single treatment-outcome pair, could establish whether the discrepancy reflects treatment modality, ancestry, or effect-size inflation.

### 4.3. Immune Regulation Variants and irAEs

HLA alleles and immune-regulatory variants form the category with the clearest mechanistic rationale: the HLA system governs antigen presentation to T cells, and functional variation may shape the autoreactive repertoires that ICIs unmask [62]. The opposing directionality of HLA-DRB1*04:01 and HLA-DRB1*15:01 within the same cohort supports this interpretation [42], and DRB1*04:01 carries the rheumatoid arthritis shared epitope, suggesting that ICI-unmasked autoimmunity may recapitulate spontaneous autoimmune disease [63]. Therefore, comprehensive class I and class II typing could contribute to a multi-marker irAE risk score, analogous to HLA-B*57:01 screening before abacavir [64].

Two *IL7* associations are notable given the role of interleukin-7 in T-cell homeostasis, where signaling promotes clonal expansion of autoreactive populations; convergent evidence at two distinct variants in two independent cohorts strengthens the case [40,41]. The *DOCK8* association with thrombocytopenia is less expected given the gene's role in lymphocyte migration [65], illustrating the difficulty of mechanism-based classification. HLA-DPB1*02 was identified as a predictor of pneumonitis in a single cohort of 42 patients, reported first as a congress abstract and subsequently as a full article [45,46]; the allele may present lung-derived antigens during PD-1 blockade, positioning pneumonitis as organ-specific and distinct from HLA-DRB1-linked systemic autoimmunity. A separate prospective cohort linked HLA-DRB4 carriage to endocrine irAEs and, in the same patients, to longer overall survival [47], consistent with the shared mechanistic basis of toxicity and response under ICI therapy. *PDCD1* rs10204525 is the only variant that acts on the direct target of ICI therapy rather than upstream, through differential miR-4717-3p binding [48,66]. *NOD2* loss-of-function variants implicate innate immunity as a novel factor in NSCLC, though the mutant group was small [49].

### 4.4. Target Pathway Signaling Variants

The *GPR68* missense variant is among the most statistically compelling novel findings in this review, predicting chemotherapy-induced peripheral neuropathy [20], a toxicity that affects as many as 60% of patients receiving chemotherapy [67], often forces dose reduction, and lacks validated predictive biomarkers. *GPR68* is a proton-sensing G protein-coupled receptor expressed in peripheral sensory neurons, where activation by acidic microenvironments modulates neuronal excitability [68]. The variants truncate the C-terminus and disrupt its three arrestin-binding motifs, which is predicted to block receptor internalization and prolong *GPR68* signaling, a gain-of-function mechanism that may sensitize sensory neurons to chemotherapy-induced stress [20]. A second, independent signal from the same cohort implicates *GRID2*, an orphan member of the ionotropic glutamate receptor family, and is the only association in this review to reach conventional genome-wide significance. Single-nucleus RNA-sequencing of human dorsal root ganglia in the same study found *GPR68* expression highest in PEP1 sensory neurons, whereas *GRID2* was expressed in satellite glial cells as well as in sensory neurons [20], so the two loci may implicate partly distinct cellular compartments of neuropathy risk rather than a single convergent pathway. Neither has been externally replicated. If confirmed, *GPR68* genotyping could identify patients for prophylactic neuroprotection or alternative regimens.

The association between *FGF14* rs4772468 and radiation esophagitis validated an earlier report [69] and implicated FGF-mediated signaling in mucosal radiation injury [50]. FGF signaling is central to epithelial repair [70], so disrupting variants may impair recovery from radiation damage.

### 4.5. Non-Characterized GWAS Loci and the Case for Unbiased Genomic Approaches

The two associations at non-characterized loci [53,54], both from Singaporean ICI-treated cohorts, require particular attention. Both fall just short of the conventional genome-wide threshold ($p=7.29\times10^{-8}$ and $6.60\times10^{-8}$ against $5\times10^{-8}$), were identified in small cohorts without

replication (n=188 and n=111), and the effect sizes (OR>17) are atypical for common germline variants. Nevertheless, these findings highlight the power of unbiased designs over candidate-gene studies. A clear example is *GRID2* rs17020773, the only association here meeting conventional genome-wide significance, which no candidate-gene approach would have anticipated.

### 4.6. Effect-Size Inflation Across the Evidence Base

Reported associations inevitably reflect a selection process: among the studies investigating a given variant, those that reach publication are often those in which stochastic variation amplified the effect size [71,72]. This is the winner's curse, and the conditions that produce it, small cohorts, many variants tested per study, and publication conditional on significance, are all present in the literature synthesized here. Our synthesis therefore inherently captures this dynamic, as shown by the empirical distribution described in Section 3.6. Correction methods work backward from the detection threshold a study had to cross for initial publication to the true effect size most likely to have produced the estimate that was reported. As detailed in Section 2.7, rather than relying on a single model, we report two complementary estimators that together define a plausible effect interval. Because most primary studies tested several variants without applying multiplicity adjustments, our derived corrections provide a conservative estimate of the extent of effect inflation.

A second and more tractable source of inflation stems from multiple testing. Among the 35 studies, 13 incorporated multiplicity corrections, yet these were seldom extended to toxicity endpoints. Two cohorts reported that no variant remained associated with toxicity after adjustment, even as their primary survival findings did [27,38]. A third applied a linkage-disequilibrium-aware adjustment that held for objective response rate and overall survival, yet no toxicity association cleared it [26]. Another two studies specified a corrected threshold in their methods but then reported uncorrected p-values for toxicity [34,36]. This methodological

asymmetry, whereby efficacy endpoints are held to a multiplicity-corrected standard to which toxicity endpoints are not held, leads to an inflated rate of apparent discoveries in the toxicity literature.

Two practical recommendations follow. Future *XRCC1* validation should pre-specify a directional hypothesis targeting a single treatment-outcome pair rather than screening multiple endpoints. More generally, a validation cohort powered purely on the published effect estimate will likely be too small to confirm it.

### 4.7. Limitations

The limitations of this review largely reflect the constraints of the underlying evidence base. Most reported associations remain unconfirmed single-study findings: 30 of 35 studies (85.7%) did not include an independent validation cohort as defined in Section 2.4, and modest sample sizes contributed to the effect size inflation quantified in Section 3.6. Furthermore, the evidence is concentrated in Asian populations (16 of 35 studies; 45.7%), which restricts generalizability to populations with different allele frequencies and linkage disequilibrium; the reference frequencies in Table 2 derive from general-population databases rather than disease-specific NSCLC cohorts (Supplementary Table S2). Three congress abstracts provided only partial reporting. Finally, the biological consequences of most variants remain uncharacterized, notably chr3:163402331 and *LOC105373202*, and because patients receive multi-agent concurrent regimens, attributing toxicity to a specific drug-gene pair carries pharmacological confounding.

Two analytical boundaries deserve consideration beyond the constraints of the primary literature. Heterogeneity across study designs, ancestry, therapeutic regimens, and endpoints precluded formal meta-analytic pooling and outcome-level certainty grading. With the exception of *PPARα* 209G>A [19] and *GRID2* rs17020773 [20], all p-values remained nominal and uncorrected for the multiple variants tested across studies. Additionally, the cohorts differed in survival selection and discontinuation policy; therefore, part of the inter-study variability

described in Section 3.6 may be attributable to baseline cohort eligibility criteria rather than pharmacogenomic differences.

Several operational aspects of the systematic review process are disclosed in the Supplementary Material: the absence of formal PRESS peer review of the search strategies, the lack of a quantified screening agreement statistic, the lack of capture-recapture coverage assessment, lack of quantitative re-synthesis, reliance on manual citation chaining, and the identification of one eligible report (Heersche et al., 2025) by journal hand-searching following formal database closure. Supplementary identification methods were part of the search design (Figure 1); this report is therefore included as a study that fell within the eligibility window but reached the review through hand-searching rather than through the database strategy.

### 4.8. Clinical Translation Roadmap

No germline NSCLC pharmacogenomic marker is currently recommended for routine pre-treatment genotyping by the CPIC, the Dutch Pharmacogenetics Working Group, or the US Food and Drug Administration. The benchmarking reported in Section 3.5 (Table 3) illustrates that candidate variants have not yet reached the evidence threshold required for clinical implementation, thereby defining the exact translational gap that this roadmap aims to address.

#### 4.8.1. Why Implementation Has Not Followed Biological Plausibility

A consistent observation across the studies included in this review is that the gap between discovery and clinical application remains substantial. Numerous biologically plausible associations have been reported, but most have been evaluated only once and in relatively small cohorts: 30 of 35 studies included no independent validation cohort, and the median cohort size was 157 patients. Differences in toxicity definitions, study design, and analytical approaches further complicate comparisons across studies and hinder replication, and only 13 of 35 studies applied any multiplicity correction. Consequently, few markers have accumulated the level of

evidence typically required for implementation in clinical practice. Notably, this pattern mirrors the early trajectory of pharmacogenetic biomarkers such as *DPYD* and HLA-B*57:01 [1,3], which became clinically actionable only after extensive validation efforts.

#### 4.8.2. Benchmarking Against the CPIC and PharmGKB Evidence Hierarchy

PharmGKB grades the evidence for a variant-drug association from level 1A, supported by a clinical guideline or an FDA drug label, down to level 4, based on preliminary evidence [11]. CPIC assigns gene-drug pairs to levels A through D, of which only levels A and B carry prescribing recommendations [10]. Mature implementation is exemplified by HLA-B*57:01 before abacavir [3], HLA-B*15:02 before carbamazepine [4], and *DPYD* before fluoropyrimidines [1,73], each supported by prospective evidence of reduced severe toxicity.

These precedents may also set an unattainable target. HLA-B*57:01, HLA-B*15:02, and *DPYD* are high-penetrance variants in single genes producing near-binary phenotypes, whereas the toxicities reviewed here are graded, multifactorial, and mechanistically heterogeneous. If susceptibility to treatment-related toxicity in NSCLC is genuinely polygenic, no single variant will accumulate the effect size and reproducibility that a CPIC level A assignment demands, and the appropriate unit of implementation is a composite score rather than a drug-gene pair. The convergent but individually modest HLA class II and *IL7* signals reported here are consistent with this architecture, which makes Phase 3 below a destination rather than an optional refinement.

#### 4.8.3. A Four-Phase Translation Roadmap

Phase 1, targeted prospective validation (12-24 months): testing of the twelve priority variants in multicenter, multi-ethnic cohorts with pre-registered single-variant hypotheses, harmonized Common Terminology Criteria for CTCAE v5 grading, and centralized genotyping, embedded within ongoing phase III NSCLC trials that have already collected biospecimens and graded

toxicity. Cohorts should be sized on the corrected estimates in Supplementary Table S3 and on the cross-ancestry allele frequencies in Table 2, which vary by more than an order of magnitude for rare *GPR68* coding variants.

Phase 2, functional validation (18-36 months, in parallel): reporter assays for *IL7*, induced pluripotent stem cell (iPSC)-derived sensory neuron models to test whether the *GPR68* C-terminal variants prolong receptor signaling, peptide-binding assays for HLA-DPB1*02 and HLA-DRB1*04:01, and confirmation of allele-specific miR-4717-3p binding to *PDCD1*.

Phase 3, composite risk scores (24-36 months): multi-variant scores combined with clinical covariates, building on the HLA polygenic score for thyroid irAEs [44] and prospective multi-gene panel implementation [74].

Phase 4, implementation and cost effectiveness (36+ months): demonstration that genotype-guided monitoring improves clinically meaningful endpoints, with cost effectiveness evaluated against the current standard care. HLA-DPB1*02 pneumonitis screening is the most plausible first candidate on clinical grounds, because pneumonitis carries the highest case fatality among irAEs and class II typing is already established in clinical laboratories; however, the association itself, currently rests on a single 42-patient cohort and would have to clear Phase 1 first.

#### 4.8.4. Implementation Considerations Specific to NSCLC

Barriers to pharmacogenomic implementation have been mapped across seven domains, from equity and evidence to payer coverage, record integration and education [75]. Three take a distinctive form in NSCLC. Most patients start treatment within days of diagnosis, so results must return within 48 hours. Ancestry-aware panels are essential, since allele frequencies for the priority candidates differ several-fold across populations and by more than an order of magnitude for the rare *GPR68* coding variants (Table 2), a bias that pervades pharmacogenomic

discovery in oncology [76]. And because somatic profiling is already routine, adding a germline panel is a marginal rather than a stand-alone cost.

## 5. Conclusions

Thirty-five studies yielded 34 associations across five categories, 30 of which were statistically significant, spanning drug transport, DNA repair, immune regulation, target-pathway signaling, and two loci with no established functional annotation. The evidence base is mechanistically coherent but not yet clinically actionable: 85.7% of studies lack independent validation, published effect sizes systematically overestimate true magnitudes, all but two p-values are nominal, and the concentration of evidence in Asian cohorts limits generalizability. Three candidates are closest to the threshold on replication and effect size (*ABCG2* rs12505410, *XRCC1* rs25487, and the *GPR68* coding variants), followed by the *IL7* variants, supported by convergent signals at two variants in two independent cohorts, and the HLA class II alleles linked to pneumonitis and endocrine irAEs, each of which rests on a single cohort. *GRID2* rs17020773 is the only association to cross the conventional genome-wide threshold, but rests on a single cohort without external replication. None reaches the evidence level required for pre-emptive testing. Closing that gap requires coordinated multi-ethnic validation embedded in existing trial infrastructure, parallel functional work, composite risk scores, and cost-effectiveness evidence. The candidate-discovery phase of this field is now mature; its implementation phase has only just begun, and this pattern extends beyond thoracic oncology.

## List of abbreviations

*ABCB1*: ATP-binding cassette sub-family B member 1
*ABCC1*: ATP-binding cassette sub-family C member 1
*ABCG2*: ATP-binding cassette sub-family G member 2
AE: Adverse event
AI: Artificial intelligence
*ALK*: Anaplastic lymphoma kinase
*ATIC*: 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase
*BRAF*: B-Raf proto-oncogene, serine/threonine kinase
*CCND1*: Cyclin D1
*CDA*: Cytidine deaminase
CI: Confidence interval
CPIC: Clinical Pharmacogenetics Implementation Consortium
CRT: Chemoradiotherapy
CTCAE: Common Terminology Criteria for Adverse Events
*CYP3A4*: Cytochrome P450 family 3 subfamily A member 4
*DOCK8*: Dedicator of cytokinesis 8
*DPYD*: Dihydropyrimidine dehydrogenase
*EGFR*: Epidermal growth factor receptor
*EPO*: Erythropoietin
*ERCC5*: Excision repair cross-complementation group 5
*FGF14*: Fibroblast growth factor 14
*GPR68*: G protein-coupled receptor 68
*GRID2*: Glutamate ionotropic receptor delta type subunit 2
GWAS: Genome-wide association study
HLA: Human leukocyte antigen
*hTERT*: Human telomerase reverse transcriptase
HWE: Hardy-Weinberg equilibrium
IARC: International Agency for Research on Cancer
ICI: Immune checkpoint inhibitor
*IL7*: Interleukin 7
irAE: Immune-related adverse event
*KRAS*: Kirsten rat sarcoma viral oncogene homolog
LD: Linkage disequilibrium
LLM: Large language model
MAF: Minor allele frequency
*MTHFR*: Methylenetetrahydrofolate reductase
*NOD2*: Nucleotide-binding oligomerization domain containing 2
NOS: Newcastle-Ottawa Scale
*NRF2*: Nuclear factor erythroid 2-related factor 2
NSCLC: Non-small cell lung cancer
OR: Odds ratio
PD-1: Programmed cell death protein 1
PD-L1: Programmed death-ligand 1
*PDCD1*: Programmed cell death 1
PharmGKB: Pharmacogenomics Knowledgebase
*PPARα*: Peroxisome proliferator-activated receptor alpha
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International prospective register of systematic reviews

*RAD51*: *RAD51* recombinase
*ROS1*: ROS proto-oncogene 1
RT: Radiotherapy
RTOG: Radiation Therapy Oncology Group
*SERPINA5*: Serpin family A member 5
SNP: Single nucleotide polymorphism
*STAT1*: Signal transducer and activator of transcription 1
SWiM: Synthesis Without Meta-analysis
TKI: Tyrosine kinase inhibitor
*TP53*: Tumor protein p53
*UGT1A1*: UDP glucuronosyltransferase family 1 member A1
VNTR: Variable number tandem repeat
WHO: World Health Organization
*XRCC1*: X-ray repair cross complementing 1

## Declarations

### Ethics approval and consent to participate

Not applicable. This review analyzed previously published, aggregated data; no new primary data were generated, and no ethical approval was required. The use of artificial intelligence in the preparation of this manuscript is declared in Section 2.9.

### Consent for publication

Not applicable.

### Availability of data and materials

All data analyzed in this review were derived from the 36 published reports of the 35 included studies cited and are tabulated in Tables 1-3 and Supplementary Material. The review protocol is publicly available on PROSPERO (CRD420261364865).

### Competing interests

The authors declare no competing interests.

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**Authors' contributions**

Conceptualization, methodology, data curation, writing of the original draft, review and editing, supervision and project administration: J.O., E.P.-R., A.E.-S. and A.R.-D. Study screening, data extraction, quality assessment, data curation and writing of the original draft: A.G.-H. Review and editing, and supervision: J.C.B., A.C., F.V.-P. and C.F. All authors read and approved the final manuscript.

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## Supplementary material

Supplementary Table S1. Study characteristics of the 35 included studies (36 reports).
Supplementary Table S2. Population allele frequencies of the priority variants across ancestry groups.
Supplementary Table S3. Winner's-curse-corrected effect estimates for the priority variants.
Supplementary Figure S1. Geographic distribution and treatment types of the 35 included studies.
Supplementary Figure S2. Newcastle-Ottawa Scale total scores of the 35 included studies.
Supplementary Figure S3. Effect size against sample size for the 27 associations reporting both a ratio estimate and an NSCLC-specific sample size.
Supplementary Figure S4. *XRCC1* rs25487 effect estimates by cohort.
Supplementary Methods. Full search strings and reporting-process limitations.
PRISMA 2020 checklist.
SWiM checklist.

*Single-file version prepared for peer review: Tables 1-3 and Figures 1-3 are embedded in the body of the text at the point where they are first cited, each in its own landscape (tables) or portrait (figures) page. The supplementary items listed above are supplied as separate additional files: Supplementary material (Tables S1-S3 and Figures S1-S4), Supplementary Methods, PRISMA 2020 checklist and SWiM checklist. High-resolution vector versions of Figures 1-3 (.svg) are available on request or at production stage.*

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- Additionalfile3PRISMA2020checklist.docx
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