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REVIEW

A Systematic Review of SNPs Screening for Platinum-Related Pharmacodynamics and Pharmacokinetics Genes in Non-Small Cell Lung Cancer for Precision Medicine

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Introduction: Traditional treatments for non-small cell lung cancer (NSCLC), such as chemotherapy, especially platinum-based regimens, often lack efficacy due to the disease's inherent heterogeneity. Precision medicine in NSCLC recognizes each tumor's unique genetic profile. Alterations in the pharmacokinetics and pharmacodynamics of platinum-based therapies significantly influence their clinical outcomes. Previous research has predominantly focused on genetic polymorphisms in genes like *Glutathione S-transferase Pi 1 (GSTP1), ATP Binding Cassette subfamily C member 2 (ABCC2), Excision repair cross-complementation group 1 and 2 (ERCC1, and/ ERCC2*), which play crucial roles in detoxification, drug transportation, and Nucleotide Excision Repair (NER). However, findings have shown considerable variability.

Methods: The analysis followed the PRISMA and STROPS Guidelines, using specific search terms including NSCLC, Chemotherapy, Polymorphisms, Single Nucleotide Polymorphisms (SNPs), *ERCC1, ERCC2, ABCC2, GSTP1*, Effectiveness, and Clinical Response. These studies were subjected to full-text screening process.

Results: Initial screening of 370 studies, comprising 275 from PubMed and 95 from EBSCO, identified 53 relevant ones, excluding those such as reviews, non-English studies, and meta-analyses. Among the genetic variants studied (ERCC1 rs11615, ERCC2 rs13181, ABCC2 rs717620, GSTP1 rs1695), GSTP1 rs1695 emerged as particularly promising, with 11 studies indicating a significant association with improved survival outcomes.

Conclusion: The integration of SNP profiling into clinical decision-making processes holds substantial potential for enhancing the personalization of NSCLC treatment strategies, thereby improving patient outcomes.

Keywords: NSCLC, chemotherapy, polymorphisms, SNPs, *ERCC1*, *ERCC2*, *ABCC2*, *GSTP1*

Introduction

Precision medicine in non-small cell lung cancer (NSCLC) is increasingly becoming a pioneering method to revolutionize cancer treatment. The foundation for modern treatment approaches in NSCLC can be traced back to 1969, when cisplatin one of the first effective chemotherapy agents was discovered. Subsequently, targeted therapies and immunotherapies were developed, leading to the occurrence of the pharmacogenomics era, which aimed to maximize efficacy and reduce adverse effects.[1,2] Traditional treatment, including chemotherapy, particularly platinum-based regimens, as well as modalities such as radiation and surgery, are often associated with limited success due to the inherent heterogeneity of the disease.[3] However, recent advances in genomics and molecular biology have shown information

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regarding the genetic alterations influencing NSCLC and patient responses to chemotherapy.[4] This information has been used for the development of specific therapies to target certain genetic mutations and predict responses to chemotherapy.[5–8] However, accessibility and affordability of innovative treatments, including targeted therapy and immunotherapy, pose significant challenges, particularly in low- and middle-income countries (LMICs).[9–11] Despite the accessibility of targeted and immunotherapy treatments, some therapies have shown minimal or no response in patients with NSCLC. In previous studies, the overall response rate has been limited when using only targeted therapy or immunotherapy, leading to the combination of biologic agents with conventional chemotherapy, such as paclitaxel and platinum-based regimens, to potentially improve treatment efficacy.[12–14]

Platinum-based chemotherapy as the first-line conventional treatment in NSCLC is widely used, particularly in patients with a wildtype or negative profile for biomarkers such *as EGFR, PD-L1, ROS1*, and *ALK* fusion.[15] Studies focusing on personalized medicine in targeted therapy and immunotherapy related to clinical outcomes such as HR and PFS are more significant compared to others on cytotoxic or conventional chemotherapy. Previous meta-analyses had shown that there was no personalized method in clinical trials for conventional chemotherapy.[16] Meanwhile, the effectiveness of platinum is varied based on genetic profiles, particularly gene markers in the pharmacokinetics and pharmacodynamics of platinum.[17–21]

The genetic profile, including polymorphism on *Glutathione S-transferase Pi 1 (GSTP1)* as detoxification enzymes and *ATP Binding Cassette subfamily C member 2 (ABCC2)* as the transporter, can influence the pharmacokinetics mechanism on platinum-based. Meanwhile, the polymorphism of *Excision repair cross-complementation group 1 and 2 (ERCC1, and/ ERCC2*) genes that play a role in Nucleotide Excision Repair (NER), is capable of influencing pharmacodynamics mechanism. This polymorphism can alter the expression level of protein and activity, leading to the clinical outcomes of chemotherapy.[22–25] The identification of genetic aberrations also allows clinicians to optimize treatment outcomes, minimize adverse effects, and enhance the prognosis for NSCLC patients. Consequently, screening these genetic markers represent a novelty that can fundamentally impact NSCLC therapy, particularly for platinum-based conventional chemotherapy, offering more effective and less toxic treatment options.[26,27]

In recent years, several databases and tools have been developed to support the analysis and interpretation of single nucleotide polymorphisms (SNPs). One of the most widely used resources is ClinVar, a publicly accessible database that aggregates information about genomic variation and its relationship to human health. Another key resource is PharmGKB, which focuses on the impact of genetic variation on drug response and provides curated information related to pharmacogenomics. In addition to these databases, various computational tools such as SIFT, PolyPhen, and MutationTaster are commonly used to predict the functional impact of SNPs. These resources play a crucial role in SNP profiling by helping to prioritize variants for further investigation and guiding clinical interpretation.

Based on the background above, this systematic review aimed to identify, assess, and summarize the single nucleotide polymorphisms (SNPs) in key genes, namely *ERCC1, ERCC2, GSTP1, and ABCC2*, to determine their potential as predictive markers for therapy outcomes in NSCLC. The analysis focused on determining which SNPs could serve as a reliable genetic marker for platinum-based therapies. The results are expected to establish a framework for SNPs screening in NSCLC patients who tested negative for genetic alterations such as *EGFR* mutations, *ALK* fusion, *ROS1* rearrangements, or *PD-L1* expression. Additionally, the personalized method aimed to enhance decisions on treatment guidance and optimize therapeutic strategies for NSCLC patients.

Materials and Methods

Literature Search Strategy and Identification

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[28] (Supplementary 1 and 2). Additionally, the reporting quality for all included studies was assessed using Checklist Guidelines for Pharmacogenomic Studies, STrengthening the Reporting of Pharmacogenetic Studies (STROPS).[29] A systematic literature review was conducted from June to July 2023, with two authors responsible for collecting and analyzing the data. We selected studies that were eligible for inclusion using the STROPS Guidelines and predefined inclusion and exclusion criteria (Supplementary 3). Literature searches were performed using two

databases, PubMed and EBSCO. The investigation was conducted to obtain relevant studies on SNPs in *ERCC1, ERCC2, ABCC2*, and *GSTP1* genes, along with their correlation to the platinum-based chemotherapy responses, including survival. Search strategies included the use of the following terms, namely NSCLC, Chemotherapy, Polymorphisms, SNPs, *ERCC1, ERCC2, ABCC2*, and *GSTP1*, including Effectiveness, and Clinical Response (Supplementary 4). The selection of keywords referred to the population, intervention/exposure, and outcomes (PICO/PECO) method. The selected population consisted of patients with lung cancer, specifically NSCLC, and the observed exposure included ERCC1, *ERCC2, ABCC2*, and *GSTP1* gene polymorphism. Meanwhile, the outcomes focused on the chemotherapy platinum-based responses such as Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), survival rate, mortality rate, and prognosis.

Study/ Literature Selection

The screening process was carried out in two stages, title and abstract, followed by full text. This systematic review included all published studies that met the inclusion criteria without time restriction. The inclusion criteria used for the literature screening process comprised human studies with NSCLC, focusing on pharmacogenetic studies detailing genotypes and physiological effects, which are chemotherapy responses. However, the exclusion criteria were review studies, including non-English and non-human, along with short communication, editorial board, expert opinion, non-platinum therapy, adjuvant/neoadjuvant chemotherapy combined with a biologic agent (multi-modality), unrelated studies, and meta-analysis.

Data Extraction and Synthesis

Data were extracted on study characteristics including design, country, number of subjects, SNPs variant (gene and *rs* number), base changes, clinical manifestation, genotyping methods, statistical value, and author. To streamline data extraction, a spreadsheet was used for collecting the results, as shown in Table 1 and the summary was presented in Table 2. Initially, the identification of clinical manifestations was carried out to facilitate data synthesis The manifestations were based on the chemotherapy responses such as RECIST. 1.1, survival rate, mortality, prognosis, or treatment response rate discussed in all studies, as fully explained in tables and figures.

Results and Discussion

Systematic Search

Based on literature search strategy, identification, and selection process, 370 studies were obtained, consisting of 275 on PubMed and 95 from EBSCO. A total of 107 studies were collected after the title and abstract screening. At this stage, the exclusion criteria were applied, focusing on editorial, unrelated studies, review, meta-analysis, non-chemo-naive, multimodality, non-human, and duplicate between two databases. Subsequently, full-text screening was carried out, resulting inclusion of 52 studies, as shown in Figure 1. After data extraction and analysis of the result, a total of 14 variants of SNPs were obtained, including *ERCC1* (rs3212986, rs11615, rs2298881), *ERCC2* (rs13181, rs1052555, rs238406, rs1799793), *ABCC2* (rs717620, rs2273697, rs3740066), and *GSTP1* (rs1695, rs1138272, rs3740066).

Main Findings

The use of comprehensive keywords, such as “non-small cell lung cancer (NSCLC)” and “chemotherapy”, is essential to identify the specific population. Additionally, the inclusion of terms such as “polymorphisms” and the genes “ERCC1”, “ERCC2”, “ABCC2”, and “GSTP1” is crucial for determining the exposure factors. The STROPS checklist guideline is applied to ensure that the included studies meet the standards expected for reporting in the field of pharmacogenetics (Online Resource 3). Among the studies included, a significant portion of pharmacogenetics studies failed to provide explanations for addressing issues such as false positive results, multiple genetic variants, several outcomes, and various assumptions regarding the mode of inheritance.[30,32,50,51,64,68] Additionally, the majority did not sufficiently address missing data were handled.[30–32,50,51,64,68] Another checklist point on STROPS is related to the *rs* number of polymorphisms, where approximately half of the studies provided the *rs* number for each genotyped SNP. Regarding

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Table 1 Polymorphism of ERCC1, ERCC2, ABCC2, and GSTP1 on NSCLC Clinical Outcomes

Study design	Polymorphism			Result and Conclusion		Population		Ref
	Genotyping Methods	SNPs		Clinical manifestation/ outcomes	Statistical Value	Sample Size	Country	
ERCC1								
Case control	PCR-RFLP and sequencing	rs3212986	C > A	CA and AA genotype increased tumor grade lymph node involvement, and metastasis	(P<0.01), r=0.99, r=0.89, r=0.96, respectively	38 cases, 38 control	Iran	[30]
		rs11615	C > T	No significant association to the clinical outcomes.	(P > 0.05)			
Cohort prospective	Sequencing	rs11615	C > T	No significant association to the chemotherapy response (CR +PR vs SD and PD)	Adjusted OR = 1.892 (0.728–4.915), P = 0.191	89 cases	China	[31]
Cohort prospective	RT-PCR	rs11615	C > T	T allele decrease the survival rate	C/T vs C/C HR= 3.73 (P=0.016), T/T vs C/C HR= 3,25 (P = 0.041)	62 cases	Spanish	[32]
Cross Sectional	PCR- RLFP	rs11615	C > T	No statistically significant to response rate	P > 0.05	285 cases	Bangladesh	[33]
Cohort prospective	Mass ARRAY	rs11615	C > T	T allele decrease the chemo response rate, and increased risk of death	OR = 0.53 (0.33–0.86), HR = 1.97 (1.20–3.34) P= 0.007, respectively	163 cases	China	[34]
		rs3212986	C > A	A allele decrease the chemo response rate, and increased the risk of death	OR = 0.44 (0.27–0.74) and HR = 1.99 (1.13–3.35) P <0.001, respectively			
		rs2298881	A > C	No statistically significant to response and risk to death	P = 0.48			
Cohort prospective	RT-PCR	rs11615	C > T	C/T and TT genotype increased the treatment response	OR 10.161; 95% CI 1.776–11.163; P = 0.001	91 cases	China	[35]
Cohort prospective	PCR- RFLP	rs11615	G > A	AA genotype increase the chemotherapy response, and decrease the risk of death	OR = 2.73 (1.21–6.18) P= 0.007 and HR = 0.38 (0.14–0.96) P= 0.03, respectively	240 cases	China	[36]
		rs3212986	C > A	No statistically significant to chemo response and risk to death	P > 0.05			
		rs2298881	A > C	No statistically significant to chemo response and risk to death	P > 0.05			
Cohort prospective	RT-PCR	rs11615	C > T	T allele significantly increase the survival	X^2 = 8.647, P=0.003	130 cases	China	[37]
Cohort prospective	MassARRAY	rs11615	C > T	T allele genotype associated with a poor response to chemotherapy and shorter survival time	OR= 0.27 (0.10–0.71), P= 0.03, HR= 2.38 (1.03–6.13), P= 0.04, respectively	226 cases	China	[38]
		rs3212986	C > A	A allele genotype associated with a poor response to chemotherapy and shorter survival time	OR= 0.36 (0.11–0.97), P= 0.03 HR = 2.14 (1.35–3.39), P= 0.005, respectively			
		rs2298881	A > C	No statistically significant to chemo response	P > 0.05			
Cohort prospective	RT- PCR	rs11615	C > T	C allele increase the chemotherapy response rate, and time to progression	X^2 = 4.284, P = 0.038		China	[39]
Cohort prospective	Multi-PCR	rs11615	C > T	No statistically significant to chemo response	P = 0.21	95 cases	China	[40]
Cohort prospective	RT-PCR	rs3212986	C > A	No statistically significant to chemo response and survival	P = 0.09	135 cases	China	[41]
		rs11615	C > T	No statistically significant to chemo response and survival	P = 0.22			
Cohort prospective	Mass ARRAY	rs11615	C > T	No significantly response to chemotherapy.	P = 0.08	187 cases	China	[42]
		rs3212986	C > A	A allele decrease response to platinum-based chemotherapy and a shorter survival in NSCLC patients.	OR= 0.18 (0.05–0.68), P<0.001 and HR = 4.71 (1.21–36.62), P = 0.01, respectively			
		rs2298881	C > A	No statistically significant to chemo response	P= 0.17			
Cohort prospective	Sequencing	rs11615	C > T	T allele increase the risk of death among ex and current smokers	P= 0.11	632 cases	China	[43]
Cohort prospective	PCR	rs11615	C > T	No statistically significant to chemo response	P= 0.46	192 cases	Italy	[44]

Cohort prospective	PCR	rs11615	C > T	T allele statistically significant association with elevated response	OR= 0.361 (0.150–0.868), P= 0.020	115 cases	China	[45]
		rs3212986	C > A	A allele Statistically significant association with descendent response	OR= 4.900 (1.765–13.604) P = 0.001			
Cohort prospective	PCR	rs11615	C > T	T allele decrease the response rate, PFS, and OS	RR= 29% vs 52%; P= 0.02, Adjusted HR= 1.60; P = 0.04, 1.54, Adjusted HR, 1.54; P=0.05, Respectively	146 cases	Netherlands	[46]
Cohort prospective	RT-PCR	rs11615	C > T	No statistically significant to chemo response	P = 0.274	26 cases	Thailand	[47]
Cohort prospective	PCR	rs11615	C > T	No statistically significant to chemo response	P = 0.65	65 cases	Italy	[48]
Cohort prospective	RT-PCR	rs11615	C > T	No statistically significant to chemo response	P = 0.087	50 cases	Egypt	[49]
ERCC2 (XPD)								
Case Control	Mass ARRAY	rs13181	T > G	G allele increase the chemotherapy response (CR+PR vs SD and PD)	OR = 2.37 (1.12–5.01), P = 0.021	506 cases, 510 control	China	[50]
		rs1052555	G > A	A allele increased the chemotherapy response (CR+PR vs SD and PD)	OR = 2.67, 95% CI: 1.12–6.36, P = 0.022			
		rs238406	G > T	GT genotype have a higher risk to develop a lymph node metastasis compared with GG genotype	OR = 1.72, 95% CI: 1.03–2.89, P = 0.040			
Cohort prospective	RT-PCR	rs13181	A > C	No statistically significant to the survival	P = 0.899	62 cases	Spanish	[32]
		rs1799793	G > A		P = 0.341			
Cohort prospective	Sequencing	rs13181	A > C	No significant association to the chemotherapy response (CR +PR vs SD and PD)	Adjusted OR = 1.599, 95% CI; P = 0.502	89 cases	China	[31]
Cross-Sectional	PCR- RFLP	rs13181	A > C	Not statistically significant to toxicity	P>0.05	180 cases	Bangladesh	[51]
Cohort prospective	Duplex PCR	rs238406	C > A	Not statistically significant to the treatment responses and survival	P= 0.66	375 cases	China	[52]
		rs1799793	G > A	A allele had poor response, and shorter OS	OR= 0.67 (0.36–0.97) P = 0.08 and HR= 1.73 (0.97 −2.92) P= 0.07, respectively			
		rs1052555	C > T	T allele had poor response, and shorter PFS	OR = 0.52 (0.37–0.96) P < 0.05 and 1.89 (1.08–3.03) P < 0.05, respectively			
		rs13181	A > C	Not statistically significant to the response and survival	P = 0.17, P = 0.28, respectively			
Cohort Prospective	RT-PCR	rs13181	A > C	Not statistically significant to the treatment responses and survival	P>0.05	398 cases	China	[53]
Cohort Prospective	MassArray	rs238406	C > A	Not statistically significant to the chemo response	OR=1.02 (0.68–1.52) P= 0.93	496 cases	China	[54]
		rs1799793	C > T	T allele associated to poor chemo responses	OR= 0.67, 95% CI=0.38–0.97			
		rs1052555	C > T	T allele associated to poor chemo responses	OR= 0.54, (95% CI= 0.35–0.96)			
		rs13181	A > C	Not statistically significant to the chemo response	OR= 0.67 (0.35–1.09) P= 0.17			
Cohort Prospective	Microarray	rs1799793	G > A	G allele associated to higher survival	HR= 1,53 CI95% 1.11–2.12, P= 0.009	218 cases	China	[55]
Cohort Prospective	PCR- RFLP	rs13181	A > C	Not statistically significant to the PFS and OS	P= 0.542	199 cases	China	[56]
Cohort prospective	PCR-RFLP	rs1052555	C > T	T allele significantly associated with better Overall Survival	Adjusted HR=0.67, 95% CI=0.45–1.00, P=0.05	382 cases	Korea	[57]
Cohort prospective	MassARRAY	rs1799793	G > A	A allele significantly associated with poorer NSCLC survival	Median OS= 19.0 (16.7–21.3), P = 0.006	445 cases	China	[58]
		rs13181	A > C	C allele significantly associated with poorer NSCLC survival	Median OS= 19.0 (16.3–21.7) P = 0.014			

(*Continued*)

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Table 1 (Continued).

Study design	Polymorphism			Result and Conclusion		Population		Ref
	Genotyping Methods	SNPs		Clinical manifestation/ outcomes	Statistical Value	Sample Size	Country	
Cohort prospective	PCR-RFLP	rs1799793	G > A	No statistically significant to chemo response	P = 0.502	93 cases	China	[59]
		rs1052555	C > T	No statistically significant to chemo response	P = 0.517			
RCT	RT-PCR	rs13181	A > C	A allele significantly less likely to respond to treatment	HR= 0.33; 95% CI, 0.13–0.83; P = 0.02	145 cases	Japan & US	[60]
Cohort prospective	RT-PCR	rs13181	A > C	Not statistically significant to toxicity	OR= 0.72; 95% CI, 0.30–1.74, P = 0.54	115 cases	China	[61]
Cohort prospective	RT-PCR	rs13181	A > C	No statistically significant to chemo response	P = 0.20	192 cases	Italy	[44]
Cohort prospective	RT-PCR	rs13181	A > C	No statistically significant to chemo response	P = 0.905	103 cases	China	[62]
Cohort prospective	RT-PCR	rs13181	A > C	No statistically significant to chemo response	P = 0.30	65 cases	Italy	[48]
		rs1799793	G > A	No statistically significant to chemo response	P = 0.82			
Cohort prospective	RT-PCR	rs13181	A > C	No statistically significant to chemo response	P = 0.202	142 cases	China	[63]
ABCC2								
Cohort Prospective	Microarray	rs717620	C > T	TT genotype increases the chemotherapy response (CR+PR vs SD and PD)	Adjusted OR= 4.493, CI = 1.728–11.682 (P = 0.002)	113 cases	China	[64]
		rs2273697	G > A	The genotypes were not substantially different between the groups				
		rs3740066	C > T					
Cohort prospective	PCR- RLFP	rs717620	C > T	T allele increased the PFS and OS	X^2=6.808, P=0.009, OR=2.182, 95% CI: 1.252–3.805, P=0.006 X^2=5.683, P=0.017, OR=2.019, 95% CI: 1.130–3.607, P=0.018, respectively	84 cases	China	[65]
Cohort prospective	MassArray	rs717620	C > T	C allele increase the chemo response	Adjusted OR= 1.84; 95% CI, 1.05–3.23, P= 0.032	445 cases	China	[66]
		rs2273697	G > A	Not statistically significant to the chemo response and toxicity	P> 0.05			
		rs3740066	C > T	T allele increase the risk of 3–4 toxicity	Adjusted OR= 2.43; 95% CI, 1.06–5.56) P= 0.034			
Cohort prospective	Mass Array	rs717620	G > A	A allele carriers have better response to chemotherapy	Additive model: OR= 0.55, 95% CI 0.31–0.96, P = 0.036; Dominant model: OR 0.41, 95% CI 0.22–0.79, P = 0.007	395 cases	China	[67]
		rs2273697	G > A	Not statistically significant to the chemo response	P = 0.357			
		rs3740066	G > A	Not statistically significant to the chemo response	P= 0.873			

GSTP1								
Cohort Prospective	Microarray	rs1695	A > G	G Allele increases the chemotherapy response (CR+PR vs SD and PD)	Adjusted OR= 2.788 CI95% (1.106–7.029) (P= 0.030)	113 cases	China	[64]
RCT	Sequencing	rs1695	A > G	G allele decrease the risk of high-grade neutropenic	P = 0.020	108 cases	United Kingdom	[68]
		rs147282497	C > T	This polymorphism not detected in this patient group				
		rs1138272	C > T	Not statistically significant to survival	P= 0.54			
		rs781659437	G > A	This polymorphism not detected in this patient group				
Cohort Prospective	Duplex PCR	rs1695	A > G	A allele showed a shorter survival and increase risk of death	HR=1.89, 95% CI (1.10–3.17)	460 cases	China	[24]
Cross Sectional	PCR- RLFP	rs1695	A > G	G Allele had significant less suffering from neutropenia and anemia, also increase the chemo response	OR= 0.31 (0.10–0.96) P= 0.043 and OR= 0.29 (0.10–0.87) P= 0.027, OR= 2.08 (1.02–4.26) p= 0.045 for genotype AG OR= 1.98 (1.02–3.87) P= 0.044 genotype AG+GG, respectively	285 cases	Bangladesh	[33]
Cohort prospective	RT-PCR	rs1695	A > G	G allele increase the chemotherapy response rate, and time to progression	X^2= 10.748, P= 0.001 and X^2= 4.548 P<0.01, respectively	91 cases	China	[35]
Cohort prospective	PCR- RLFP	rs1695	A > G	G allele increase the chemotherapy response (CR+ PR), and lower risk of death	OR=2.18 95% CI (1.16–4.12) p= 0.009 and HR= 0.48; 95% CI (0.25–0.93), P=0.02 respectively	282 cases	China	[69]
Cohort prospective	PCR- RLFP	rs1695	A > G	G allele decrease the chemotherapy response and increase risk of death	OR = 0.13 (0.04–0.37) P < <0.05 and HR = 4.35 (1.40–17.92) P= 0.005, respectively	322 cases	China	[70]
Cohort prospective	PCR- RLFP	rs1695	A > G	G allele increase the PFS and OS	OR=2.295, 95% CI: 1.332–3.954, P=0.003 and OR=1.910, 95% CI: 1.161–3.144, P=0.011, respectively	84 cases	China	[65]
Cohort prospective	PCR- RLFP	rs1695	A > G	G allele increase the chemo response, and decrease risk of death	OR = 4.07 (1.06–25.06) P = 0.03 and HR = 0.07, 95% CI = 0.01–0.34) P <0.001, respectively	141 cases	China	[71]
Cohort prospective	PCR- RFLP	rs1695	A > G	G allele affect the chemotherapy response, and OS	OR= 0.37 (0.18–0.71) P= 0.001 and HR= 0.51 (0.28–0.94) P= 0.02, respectively	308 cases	China	[72]
Cohort prospective	RT-PCR	rs1695	A > G	A allele significantly increased response in advance	OR= 3.961; 95% CI, 1.531–10.245; P = 0.005	158 cases	China	[73]
Cohort prospective	RT-PCR	rs1695	A > G	Not statistically significant to toxicity	P >0,05	47 cases	China	[74]
Cohort prospective	RT-PCR	rs1695	A > G	G allele significant associations with response rate	OR= 4.302 CI95%(1.193–15.515) P= 0.026	97 cases	China	[75]
Cohort prospective	RT-PCR	rs1695	A > G	No statistically significant to chemo response	P = 0.79	262 cases	China	[76]
Cohort prospective	RT-PCR	rs1695	A > G	GG was correlated with a good response to chemotherapy and improved the OS of advanced NSCLC patients.	OR= 2.77 (1.14–6.64) P= 0.01	244 cases	China	[77]

Abbreviations: SNPs, Single Nucleotide Excision Repair; RT, Reverse Transcription; PCR, Polymerase Chain Reaction; RFLP, Restriction Fragment Length Polymorphism; RCT, Randomized Controlled Trial; OS, Overall Survival; PFS, Progression Free Survival; OR, Odds Ratio; HR, Hazard Ratio; aHR, adjusted Hazard Ratio; CI, Confidence Interval.

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Table 2 Resume of Single Nucleotide Polymorphism and the Interpretation Related to Clinical Outcomes

No	SNP	Genotype	Total Articles	Outcomes Interpretation	n
ERCC1					
1	rs3212986	C > A	7	No statistically significant to chemotherapy response and/survival	2
				Mutant Allele decrease the chemotherapy responses and/ survival	5
2	rs11615	C > T / G > A	20	No statistically significant to chemotherapy response and/survival	9
				Mutant Allele increase the chemotherapy responses and/survival	2
				Mutant Allele decrease the chemotherapy responses and/ survival	7
				Wildtype Allele increase the chemotherapy responses and/ survival	2
3	rs2298881	A > C / C > A	4	No statistically significant to chemotherapy response and/survival	4
ERCC2					
1	rs13181	T > G / A > C	15	No statistically significant to chemotherapy response and/survival	12
				Mutant Allele increase the chemotherapy responses and/ survival	2
				Mutant Allele decrease the chemotherapy responses and/ survival	1
2	rs1052555	G > A / C > T	5	No statistically significant to chemotherapy response and/survival	1
				Mutant Allele decrease the chemotherapy responses and/ survival	2
				Wildtype Allele increase the chemotherapy responses and/ survival	2
3	rs238406	G > T / C > A	3	No statistically significant to chemotherapy response and/survival	2
				Mutant allele increased risk of metastasis and increased susceptibility to NSCLC in smokers.	1
4	rs1799793	G > A / C > T	7	No statistically significant to chemotherapy response and/survival	3
				Mutant Allele decrease the chemotherapy responses and/ survival	4
ABCC2					
1	rs717620	C > T / G > A	4	Mutant Allele increase the chemotherapy responses and/ survival	3
				Mutant Allele decrease the chemotherapy responses and/ survival	1
2	rs2273697	G > A	3	No statistically significant to chemotherapy response and/survival	3
3	rs3740066	C > T / G > A	3	No statistically significant to chemotherapy response and/survival	2
				Mutant allele increases the risk of toxicity	1
GSTP1					
1	rs1695	A > G	15	No statistically significant to chemotherapy response and/survival	2
				Mutant Allele increase the chemotherapy responses and/ survival	11
				Mutant Allele decrease the chemotherapy responses and/ survival	2
2	rs1138272	C > T	1	No statistically significant to chemotherapy response and/survival	1
3	rs147282497	C > T	1	Not detected in the population	1
4	rs781659437	G > A	1	Not detected in the population	1

polymorphisms, the majority of the studies included used alternative names such as C3972T, C-24T, or G1249A.[64–66] Consequently, this systematic review conducted data extraction and summarized results using the *rs* numbers for individual polymorphisms.

The main objective is to investigate the impact of genetic variations on chemotherapy responses, with potential outcome measures including survival rates, mortality, treatment, and RECIST 1.1 criteria. During the data extraction process, various clinical manifestations were observed, which influenced the results. Polymorphisms in *ERCC1* in 12 studies were associated with decreased or increased chemotherapy responses and survival rates.[30,32,34–37] Meanwhile, 15 studies reported non-statistically significant associations with chemotherapy responses and survival rates.[30–33,36] The majority of polymorphisms in *ERCC2*, comprising 18 studies, did not show statistically significant correlations with platinum-based chemotherapy responses.[44,48,53,59,61–63] Mutant alleles of *ABCC2* and *GSTP1* polymorphisms were found

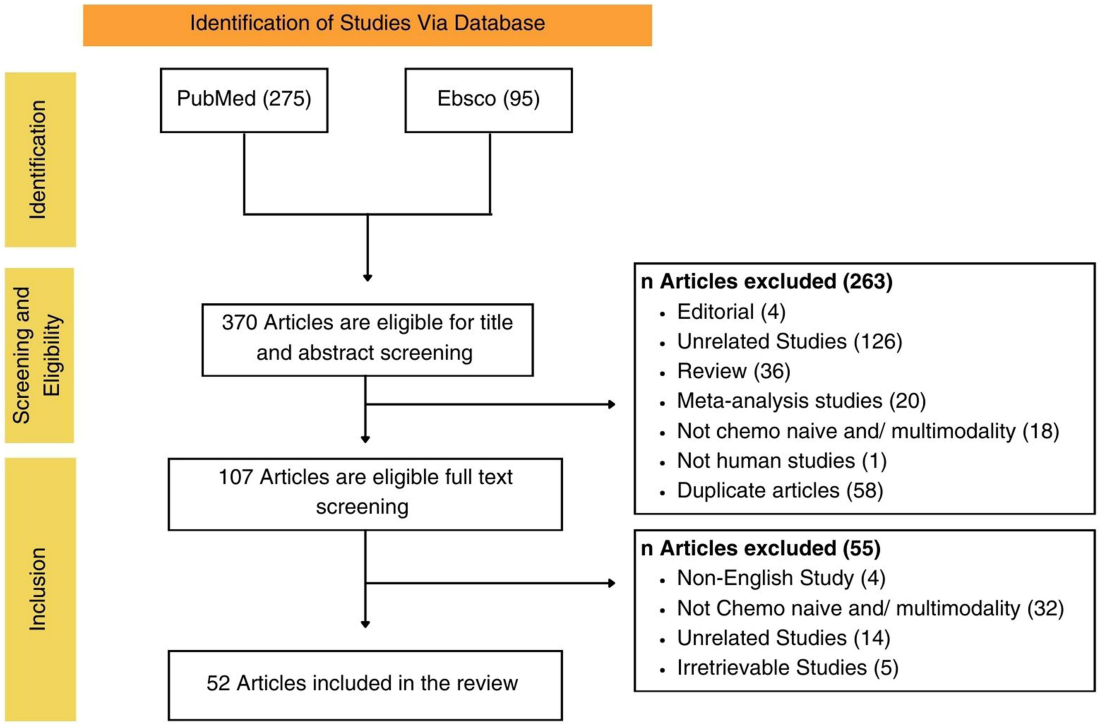

Figure 1 Research Flowchart.

to potentially enhance chemotherapy responses and improve survival rate,[33,65–68] as shown in Table 1. This suggested that SNPs variants could have a significant impact on protein structure, potentially leading to the upregulation or downregulation of protein formation or altering gene expression levels.[78–82] The results showed promise as a marker for personalized medicine, particularly in early genetic screening for NSCLC cases before initiating platinum-based therapy.

Implications of These SNPs for NSCLC Clinical Response

Cancer is the leading cause of mortality rate globally, accounting for approximately 10 million deaths in 2020.[83] Ranking as the first cancer-related fatalities, the issue of lung cancer is related to the high incidence of new cases with low survival or elevated mortality rates. Moreover, survival rates have shown a significant decreasing trend, ranging from 94% to 91% and 78%, from the first to the third year, respectively.[84] The fifth-year relative survival rate for NSCLC as a whole remains extremely low at 24%.[85] Platinum-based chemotherapy, as a first-line treatment used in NSCLC patients with wildtype profiles on *EGFR* gene, has been found to show varying responses. Previous studies have shown that the Objective Response Rate (ORR) for platinum-based first-line chemotherapy ranged from 29.7% to 46.7%, while others reported a significant proportion between 0% and 80%.[86–88]

The variability in responses among patients receiving platinum-based chemotherapy is attributed to factors such as the clinical status or the influence of genetic polymorphisms on genes in the pharmacodynamics or pharmacokinetics, as shown in Figure 2.

According to the CPIC database, ERCC1 has a D level of evidence for cisplatin, and GSTP1 also has a D level for several agents, including cyclophosphamide, oxaliplatin, epirubicin, and fluorouracil. Additionally, ABCC2 and GSTP1 are not listed in the CPIC gene-drug database. A D level of evidence means that there are few published studies, the clinical significance is unclear, the mechanistic basis is weak, or the data is conflicting. Since these genes are not commonly tested in clinical settings, further research is needed to strengthen the evidence base. This review discusses SNPs in *ERCC1* and *ERCC2* genes related to the pharmacodynamics of platinum-based chemotherapy, including SNPs in *ABCC2* and *GSTP1* genes related to the pharmacokinetics of platinum-based drugs. All of these genes show the potential

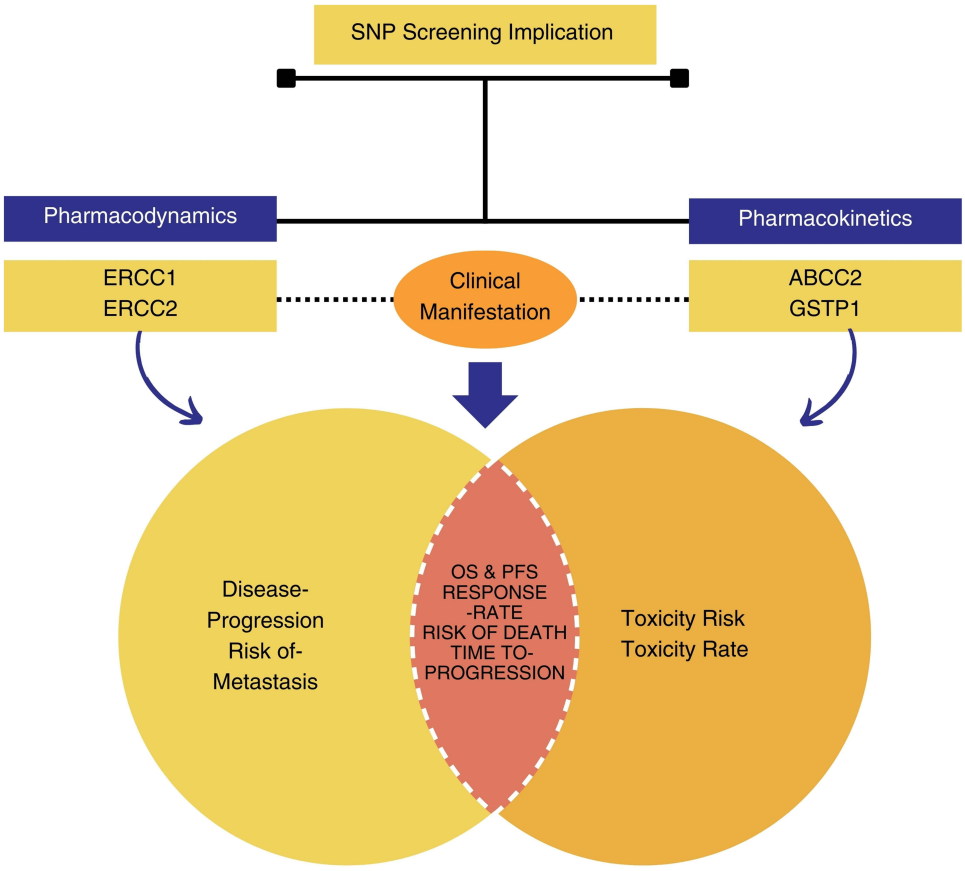

Figure 2 Single Nucleotide Polymorphism Screening Implication on Non-Small Cell Lung Cancer.

to influence clinical outcomes, including Overall Survival (OS), Progression-Free Survival (PFS), the risk of mortality, and Time to Progression.[24,30,32,36,63,64,89] Clinical manifestations, such as disease progression and the Risk of Metastasis, are specifically associated with *ERCC1* and *ERCC2* genes,[30,50] and the risk and rate of toxicity are related to *ABCC2* and *GSTP1* genes[66] as shown in Figure 2.

From the review results, we can see that studies on ERCC1 that produced significant statistics mostly had odds ratios (OR) and hazard ratios (HR) that were not very large (ranging from 0 to 1). Clinically, this suggests that the impact of these SNPs on clinical outcomes is likely not substantial, although one study reported an OR of 10.161 with a p-value of 0.001.[35] A similar situation is observed with ERCC2, while GSTP1 and ABCC2 had larger OR and HR values. However, the clinical relevance of these numbers also depends on factors such as sample size, study design, and biological plausibility.

In addition, it is important to acknowledge that ethnic variation can significantly influence the frequency and clinical impact of pharmacogenetic polymorphisms. For example, according to the PharmGKB and gnomAD databases, allele frequencies for several SNPs in ERCC1, ERCC2, ABCC2, and GSTP1 differ across populations. The ERCC1 rs11615 C allele, for instance, has been reported to be more prevalent in East Asian populations compared to Europeans or Africans, which may affect its predictive value for platinum response across different ethnic groups.[90,91] However, in our systematic review, stratified analyses based on ethnicity were not feasible due to inconsistent reporting of ethnic background and limited population-specific data. Nonetheless, we recognize that functional consequences of SNPs are not solely determined by allele frequency, but also by the nature of the nucleotide substitution, which can lead to changes in codon usage, amino acid sequence, or protein structure. These considerations underscore the importance of ethnicity-aware pharmacogenomic research and the need for further population-specific studies before SNP-guided therapy can be generalized to diverse clinical settings.

Molecular Mechanisms of ERCC1, ERCC2, ABCC2, and GSTP1 SNPs to Clinical Outcomes in NSCLC

ERCC1 and *ERCC2* genes encode proteins that play a significant role in the unwinding processes within the NER mechanism,[92,93] as shown in Figure 3. Alterations in NER mechanism activity, caused by SNPs, can impact responses to platinum-based chemotherapy,[93–95] serving as predictive markers for chemotherapy responses. This review compiled 31 studies discussing *ERCC1*, with 7 focusing on rs3212986, 20 on rs11615, and 4 on rs2298881. The results show that *ERCC1* rs11615 has the largest number of studies, indicating prominence as a major focus due to relevance in clinical manifestations, as shown in Table 2. However, a total of 9 studies related to *ERCC1* rs11615 were identified, which did not show statistically significant associations with platinum-based clinical outcomes. Among the 7 studies reviewed, the mutant allele of rs11616 was associated with decreased clinical outcomes and shorter survival in NSCLC patients treated with platinum-based therapy. In the molecular mechanism of *ERCC1* rs11615 was found to start from the substitution of Cytosine (C) with Thymine (T), resulting in the modulation of *ERCC1* expression levels. Meanwhile, in the *ERCC1* C8092A (rs3212986), situated in the 3'-untranslated region (3'-UTR), the presence of the A allele on rs3212986 was associated with high *ERCC1* expression, playing a significant role in transcription and translation processes.[96–98] This alteration affected DNA repair processes, as high activity caused by the increase in *ERCC1* expression level diminished the efficacy of platinum-based therapy.[96]

A total of 30 studies were compiled for *ERCC2/ XPD*, with 15 focusing on rs13181, 5 on rs1052555, 3 on rs238406, and 7 on rs1799793. The SNPs on *ERCC2*, specifically rs13181, have been extensively investigated, indicating a significant change from A to C, as shown in Table 2. This alteration leads to a change in the amino acid produced,

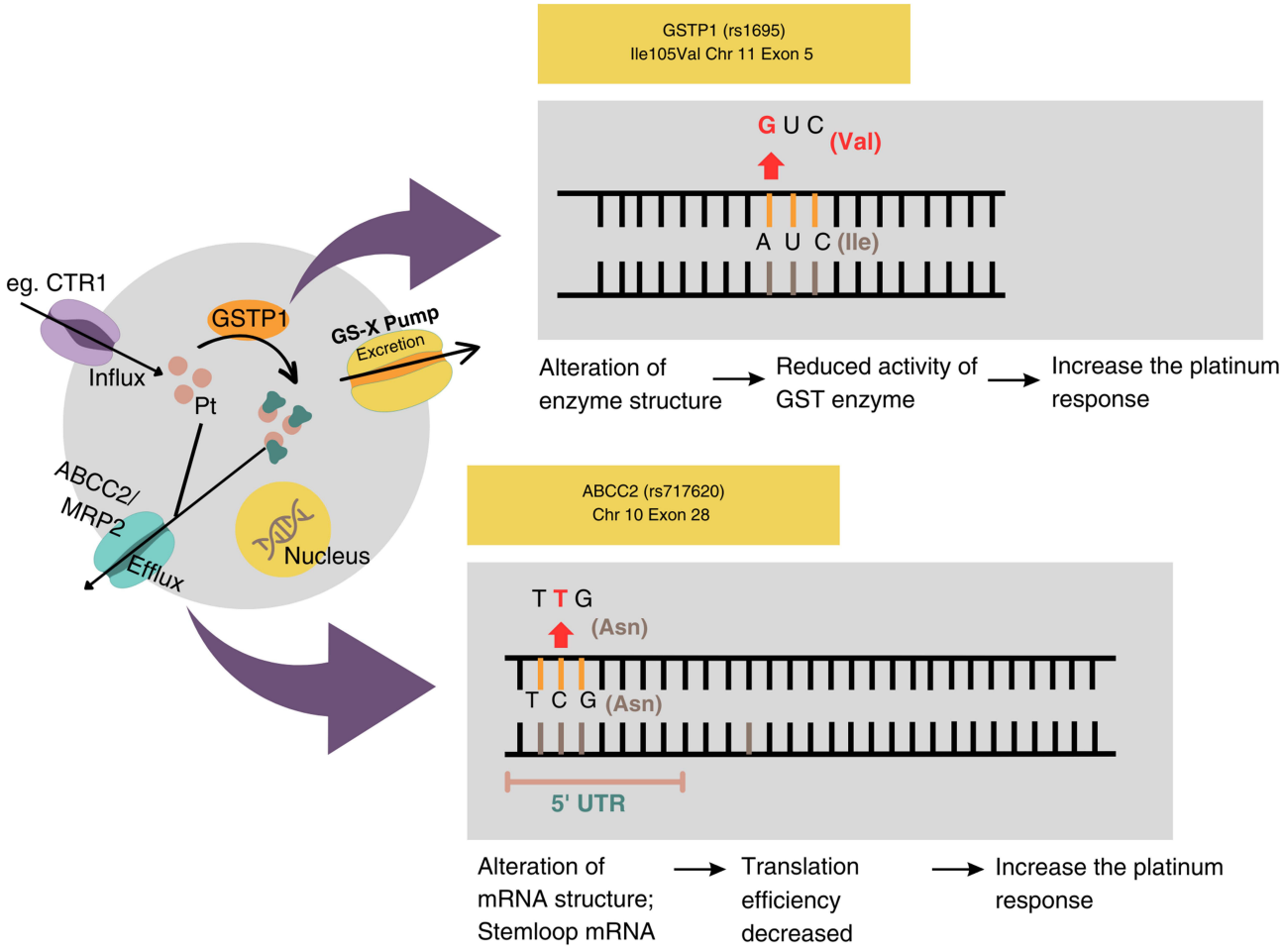

Figure 3 Single Nucleotide Excision Repair on *ERCC1* and *ERCC2*.

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shifting from Lysine (Lys) to Glutamine (Gln)[99] as shown in Figure 3. However, 12 out of the 15 studies reviewed reported non-statistically significant results regarding the association between *ERCC2* rs13181 and the clinical outcomes or survival rates of NSCLC patients receiving platinum-based chemotherapy. These results suggested that the specific SNPs are not essential predictors of treatment response or patient survival in platinum-based chemotherapy for NSCLC. Subsequently, *ERCC2* rs1799793, which ranks second in terms of the number of *ERCC2* genes studies, has shown a balanced outcome. The results are evenly distributed between studies reporting non-statistically and statistically significant association of the mutant allele with a decrease in responses to platinum-based chemotherapy. This suggests a complex relationship between *ERCC2* rs1799793, affecting the clinical outcomes or treatment responses. The *ERCC1* rs1799793 is characterized by a change from G to A and the resulting amino acid transitioned from Aspartic Acid (Asp) to Asparagine (Asn).[58] Both rs13181 and rs1799793 are common non-synonymous SNPs, located within the *ERCC2* coding sequence, with specific functions that impact the NER pathway by modulating mRNA expression.[60,100] These changes in amino acids have the potential to modify protein expression levels and influence the capacity for DNA damage repair, which is a fundamental process in NER.[22] Specifically, the enhanced functionality of NER associated with the mutations is correlated with reduced chemotherapy response.[100]

In a study conducted on a European population, a statistically significant trend was observed for the allele G → T on rs238406, which affected *ERCC2* mRNA expression (Ptrend = 0.011). However, in the Chinese Han in Beijing (CHB) population, there was only a borderline significance (Ptrend = 0.098).[101] Thus, phenomenon occurred due to the presence of linkage disequilibrium with rs13181 or other potentially functional SNPs. In this review, rs238406 was observed to be more closely associated with the risk of NSCLC, although there were no statistically significant correlations with chemotherapy response.[50,53,54,102] The results provided valuable information on the intricate relationship between genetic variations in *ERCC2* and their impact on the NER pathway, affecting the response to platinum-based chemotherapy.[103]

In pharmacokinetics, there are several essential processes, including absorption, distribution, metabolism, and elimination such as detoxification.[104,105] Numerous genes have shown significant association with these mechanisms, where genetic polymorphisms cause alterations in protein expression, affecting the rate of pharmacokinetic processes such as metabolism (*CYP* genes), detoxification (*GSTs* genes), or drug concentration at target sites when genetic variants impact transporter proteins like *ABC* transporters.[77,106,107] Among the essential genes, *GSTP1* is responsible for encoding Glutathione enzymes,[69,72,77,108–110] while *ABCC2* is used for coding the *ABC* transporter protein.[25,111–113] These genes play significant roles in pharmacokinetic process, influencing detoxification rates and facilitating the transport of active compounds such as platinum-based compounds, respectively.

GSTP1 is the primary Phase II detoxification enzyme predominantly located in the cytosol, which facilitates the bonding of electrophilic substances with glutathione (*GSH*), showing peroxidase and isomerase functions. This enzyme suppresses the activity of Jun N-terminal kinase, thereby protecting cells from death induced by hydrogen peroxide (H_2O_2). *GSTP1* possesses the ability to non-catalytically bind to a diverse array of naturally occurring and external ligands.[114] Furthermore, it plays a specific role in the detoxification process of platinum compound, which effectively captures and deactivates cisplatin, using two exposed cysteines. This phenomenon results in the interlinking of protein subunits, retaining the capability to perform GSH-conjugation activities.[115] Genetic polymorphism at *GSTP1* rs1695, situated on chromosome 11 in exon 5, induces an alteration in the amino acid produced, replacing isoleucine with valine (Ile105Val). This change includes a transition from A to G in the base pair, leading to the suppression of protein synthesis and decreased *GSTP1* enzyme activity. As shown in Figure 4, the decrease in *GST* activity causes an increase in platinum-based chemotherapy responses.[116,117] In this review, a total of 18 studies were investigated, focusing on the impact of *GSTP1* polymorphisms, as shown in Table 2. Based on the results *GSTP1* rs1695 was the most extensively investigated, with 15 studies dedicated to the exploration. Other variations such as rs1138271, rs147282497, and rs781659437 had only one study each. Furthermore, rs1695 was found to be statistically significant in 11 cases, indicating that the presence of the mutant allele (AG or GG genotype) was associated with increased platinum-based chemotherapy responses and enhanced survival, as shown in Table 2.

Regarding *ABC* transporters, particularly the *ABCC2/MRP* genes, a total of 10 studies were identified, where 4 focused on *ABCC2* rs717620, 3 on rs2273697, and 3 on rs3740066, as shown in Table 2. Based on the results, *ABCC2* rs717620 showed that the presence of the mutant allele was associated with improved chemotherapy responses and

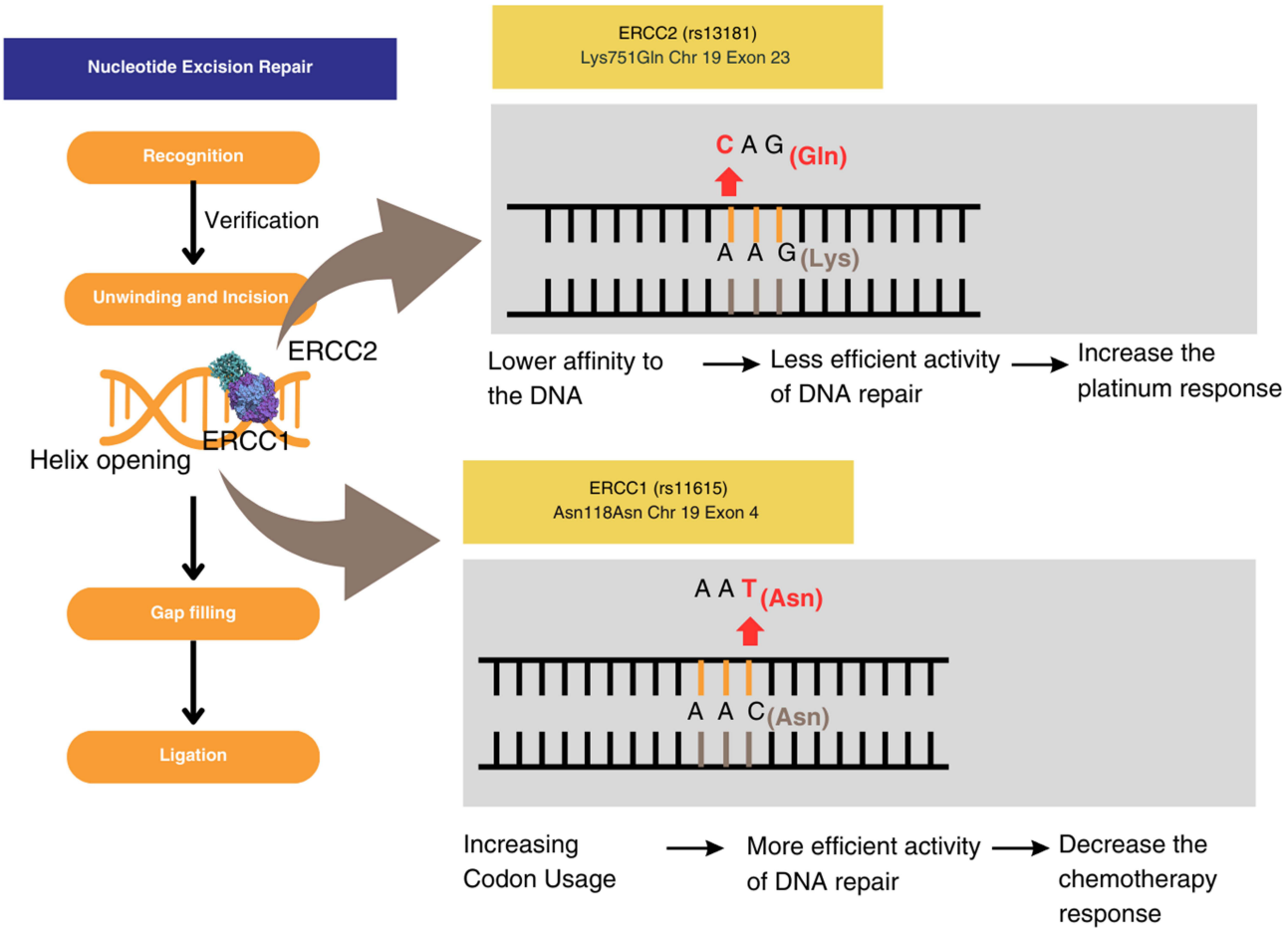

Figure 4 Single Nucleotide Excision on *GSTP1* and *ABCC2*.

enhanced survival rates. However, in one remaining study, the mutant allele was related to a decrease in survival rates among NSCLC patients treated with platinum-based chemotherapy. At the molecular level, *ABCC2* showed low expression in normal lung tissue but had high expression in lung cancer. The ABCC2 rs717620 polymorphism, situated within *ABCC2* transcript promoter, 5' UTR, included a –24C > T variant that could potentially reduce *ABCC2* expression, particularly in tumour tissue. This phenomenon described the observed suppression of drug resistance and the enhancement of treatment responses[112,118] as shown in Figure 4. However, the nonsynonymous rs2273697 (Val417Ile) and the silent rs3740066 (Ile1324Ile) polymorphisms did not show statistical significance in relation to chemotherapy responses.

Besides SNPs, Copy Number Variant (CNV) also influence clinical outcomes. When SNPs and CNVs occur at the same location, they can affect clinical outcomes.[119,120] These involve larger sections of the genome being duplicated or deleted. CNVs can change the dosage of gene products (eg, more or fewer copies of a gene), which can also influence clinical traits, such as disease risk or drug metabolism.[121] For instance, a study demonstrated that a deletion in the TBX6 gene led to an overestimation of the impact of SNPs on the hypomorphic allele. This study also generalized a model to explain calculation bias or distorted significance in association studies caused by CNVs at specific loci. Moreover, the overlap between disease-associated SNPs from published GWAS and common CNVs and pathogenic/likely pathogenic CNVs was significantly higher than random distribution, suggesting that co-occurrence of CNVs and SNPs at the same locus can significantly influence data interpretation and the potential outcomes of GWAS.[119]

In this study, several CNVs were observed at the same loci as important SNPs, including ERCC1 rs11615, ERCC2 rs13181, ABCC2 rs717620, and GSTP rs1695, and they exhibited molecular effects. For example, the NSV3163036 on ERCC1 impacts not only the coding sequence but also the 5' UTR and intron regions, which could alter gene expression

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or splicing.[122] Similarly, CNV on ERCC2 NSV2785402, GSTP1 (NSV555269, NSV468606), and ABCC2 NSV3155816 have the molecular effect on both the coding sequence regulatory regions, potentially modifying function.[123–129] While the molecular impacts of these SNPs are well documented, their interplay with CNVs at the same loci may amplify or mitigate their effects. To fully understand how CNVs influence the functional impact of SNPs, further research using methods designed to assess these combined effects is necessary.

Role of SNP Screening in NSCLC Precision Medicine

Research and development related to cancer treatment have made significant advancements. This development was initially observed in 1969 when platinum-based chemotherapy, particularly cisplatin, showcased promising efficacy in treating NSCLC. In 1995, platinum-based therapy was discovered as a significant contributor to increased survival rates among NSCLC patients. Subsequently, in 2004, the introduction of Tyrosine Kinase Inhibitors (TKIs) as targeted therapies customized to *EGFR* mutation profiles offered an essential contribution, with drugs such as gefitinib, marked a significant milestone. Erlotinib also gained approval as a second-line therapy for *EGFR* mutation-positive cases. In 2015, advanced medications such as Crizotinib showed significant effectiveness in managing *ROS1*-rearranged NSCLC, enriching the therapeutic landscape for the disease. Currently, there is continuous advancement in medication development for NSCLC, guided by genetic profiling for personalized treatment methods.[1] The standard for cancer treatment has shifted towards the use of biological agents such as targeted therapy and immunotherapy. However, platinum-based chemotherapy, a conventional cytotoxic agent, continues to be a widely used first-line treatment option Despite these numerous applications, the effectiveness and toxicity rates of platinum-based chemotherapy have shown significant variation. SNPs on several genes, particularly those that play essential roles in the pharmacokinetic or pharmacodynamic mechanisms of platinum-based chemotherapy, have become potential predictive markers for treatment responses. This has led to the application of SNPs screening to conventional chemotherapy regimens based on genetic profiles of patients. Consequently, patients who test negative for established biomarkers such as *EGFR, PD-L1, ALK* fusion, *ROS-1*, and receive chemotherapy, are administered the most suitable chemotherapy agents based on their genetic profiles.[130] This method aims to enhance the precision and efficacy of chemotherapy while minimizing the risk of adverse effects for patients.

Recent reports suggest that individual polymorphisms have relatively modest effects on clinical outcomes. This shows the need to adopt a more comprehensive method, including polygenetic, phenotypic, epidemiological, and clinical variables to accurately predict the prognosis of NSCLC patients receiving platinum-based chemotherapy.[131,132] Based on a previous study conducted in California, a potential therapeutic algorithm for NSCLC has been developed, using *ERCC1* gene expression levels.[130] The results of the comprehensive dataset including pharmacogenomics study on NSCLC, focusing on platinum-based chemotherapy and essential genes such as *ERCC1, ERCC2, ABCC2*, and *GSTP1*, have gained significant attention. Therefore, this systematic review aimed to construct a potential algorithm as a framework for personalized medicine methods in NSCLC therapy.

Challenges and Limitations of SNP Screening in Clinical Practice

Challenges and limitations of SNPs screening in clinical practice include complexities related to result interpretation, standardization of testing methods, and the need for large-scale, diverse datasets to establish robust associations. This is in line with the persistent demand for human resources in the field of genetic interpretation, where education is continually developed. Additionally, integrating SNPs data into routine clinical decision-making processes can be challenging, requiring adequate guidelines and tools for healthcare professionals. Ethical and privacy concerns regarding genetic information, along with cost-effectiveness considerations, pose significant limitations. Although SNPs offer valuable insights, their effectiveness is limited by the entire genetic landscape, requiring a comprehensive method that incorporates multiple genetic and non-genetic factors for a more accurate clinical prognosis. SNPs show complexity, indicating that an impact in one population is not essential for replicating another. This genetic diversity poses a significant challenge, showing the need for studies that are personalized and comprehensive.

Furthermore, ethical and privacy concerns remain a significant barrier to the clinical implementation of pharmacogenomics. Handling sensitive genetic data requires strict adherence to confidentiality, informed consent, and responsible

data sharing practices. There is also a risk of genetic discrimination and stigma if data are not managed carefully. As pharmacogenomic testing becomes more accessible, robust regulatory frameworks and ethical guidelines are crucial to ensure patient trust and protect individuals' rights.

Methodologies and Molecular Technique for SNP Screening

SNPs have significant implications in genetic disease, although recent methods, such as DNA microarrays, qPCR, and sequencing are characterized by intricate procedures. The methods are expensive and apply sophisticated instruments, leading to suboptimal results in clinical settings, particularly regarding multiple SNPs associated with genetic diseases. A previous study conducted in China introduced an innovative point-of-care testing (POCT) system, namely the Amplification Refractory Mutation System (ARMS) coupled with gold magnetic nanoparticles (GMNPs) and lateral flow assay (LFA). This innovation was collectively referred to as the ARMS-LFA system, offering a cost-effective, user-friendly, and highly sensitive method, enabling the uniform detection of multiple SNPs concurrently. The results showed a significant potential as a POCT tool for identifying multiple SNPs correlated with genetic disease.[133] Another study on SNP genotyping analysis for clinical applications investigated an oligo-nucleotide array-based method designed for gene-specific SNP genotyping. The results showed that the method, recognized for cost-effectiveness and high-throughput capabilities, had both high sensitivity and a level of accuracy comparable to direct sequencing. To validate accuracy and efficiency, a comparison was made with *BRCA1* gene model, in relation to breast and ovarian cancer predisposition.[134] Typically, efforts are directed towards identifying and establishing the most significant SNPs as a genetic marker for diagnosis and therapy selection. However, there are situations where the analysis of unidentified SNPs is essential to ensure a comprehensive interpretation. Conventional sequencing, which is highly informative, is often cost-prohibitive. In a recent study, an innovative method for the fluorometric detection of both known and unknown SNPs was introduced based on optimizing the well-established principle of signal loss or gain, using a significantly reduced number of matched or mismatched probes.[135]

Conclusion

In conclusion, this systematic review showed essential information regarding SNPs in *ERCC1, ERCC2, GSTP1, and ABCC2*, with their impact on NSCLC therapy outcomes, particularly with platinum-based chemotherapy. Based on the results, *ERCC1* rs11615, *ERCC2* rs13181, *ABCC2* rs717620, and *GSTP1* rs1695 were the most frequently investigated SNPs. Among these genes, *GSTP1* rs1695 showed significant potential, where 11 studies indicated an association with clinical outcomes and survival in NSCLC patients. Moreover, the integration of SNPs profiling into clinical decision-making substantially improved treatment personalization. By identifying the most appropriate genetic markers, clinicians could optimize therapy selection, enhancing both efficacy and safety. This correlated with the broader trend towards precision medicine in NSCLC, offering opportunities to enhance patient outcomes and minimize adverse effects.

Data Availability Statement

The data available in supplementary material.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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