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Optimising Systemic Therapy in Oncology: A Step Ahead in the Application of Pharmacogenetics, A Narrative Review

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Abstract

Elucidating the pharmacokinetics of anticancer agents is essential for optimising their safety and therapeutic efficacy. Pharmacogenetics and pharmacogenomics (PGx) provide a framework for understanding individual variability in drug response and minimising adverse effects by analysing genetic variants that affect drug-metabolising enzymes and membrane transporters. In oncology, where safety and efficacy are critical, personalised treatment guided by PGx markers and clinical recommendations is gaining increasing importance. Variants such as *CYP3A4*14*, **1*, **18* and *ABCB1* 1236CC were associated with reduced imatinib efficacy and an elevated risk of toxicity. *CYP2D6*17*, **29*, **4*, **10*, and **41* alleles were linked to diminished tamoxifen efficacy, while *CYP2D6*17*, **41*, **10*, and **5/*5* were reported in relation to various stages of relapse. Genotypes *GSTP1* rs1695 c.313A>G (AG and GG), *ABCC1*(c.3173G>A and rs9332430), *ABCB1* (c.1236C>T and 3435C>T), *ABCC2* (–24C/T, rs2804398, and +9383C>G), as well as *ABCC4* rs943288, were associated with increased toxicity from platinum-based therapies. Variants *UGT1A1*28*, **6* and *UGT1A7* were implicated in irinotecan-related toxicity. Additionally, *DPYD*2A* (rs3918290), **13* (rs55886062), rs67376798, and HapB3 (rs75017182) were strongly associated with severe fluoropyrimidine-related toxicities and increased treatment-related mortality. As PGx research advances, its integration into routine oncology practice will be essential for optimising therapeutic outcomes and supporting a more individualised approach to cancer treatment.

Keywords: Pharmacogenetics, Pharmacogenomics, Cancer, Chemotherapy

1. INTRODUCTION

The International Agency for Research on Cancer assesses and underscores the increasing impact of cancer across various nations.In 2022, an estimated 20 million new cancer cases were recorded globally, resulting in 9.7 million deaths. By 2050, the global incidence of new cancer cases is projected to exceed 35 million, representing a 77% increase compared to 2022.However, the majority of countries do not provide sufficient financial support for essential cancer treatment and palliative care services as integral components of universal health coverage [1]. The integration of multiple therapeutic modalities—including surgery, radiotherapy, and chemotherapy—has led to reduced mortality rates and improved survival outcomes in cancer patients. Given that cancer is fundamentally a genetic disease, chemotherapy has progressively evolved toward targeted therapies that specifically interfere with the genetic mechanisms driving neoplastic growth. Although these selective treatments help reduce therapy-related side effects, they, like conventional chemotherapeutic agents, can still contribute to the development of drug resistance and may be influenced by drug–drug interactions (DDIs), ultimately diminishing therapeutic efficacy [2]. Furthermore, various cancer therapy strategies can cause side effects and may lead to adverse events (AEs) [3]. AEs not only increase the cost of treatment but are also associated with reduced patient adherence to therapeutic regimens. Moreover, certain adverse drug reactions are known to be linked to individual genetic variability [4].

Genomics, a discipline within the OMICS sciences, focuses on genome sequencing to identify genetic variations and mutations that may contribute to disease onset or progression. Elucidating the pharmacokinetics (PKs) of anticancer agents is essential for optimising their safety and therapeutic efficacy, as variations in absorption, distribution, metabolism, and excretion can significantly influence therapeutic outcomes. In this context, pharmacogenetics/pharmacogenomics (PGx) enables the assessment of variability in drug response and the reduction of AEs by analysing interactions between genetic variations and drug-metabolising enzymes (DMEs) or transporter proteins [5, 6]. Considering the importance of safety and efficacy in systemic cancer therapy, personalised treatment guided by PGx markers and clinical guidelines is gaining increasing prominence in oncology [7]. Fig. 1 illustrates the impact of genetic polymorphisms on drug safety and efficacy in cancer therapy.

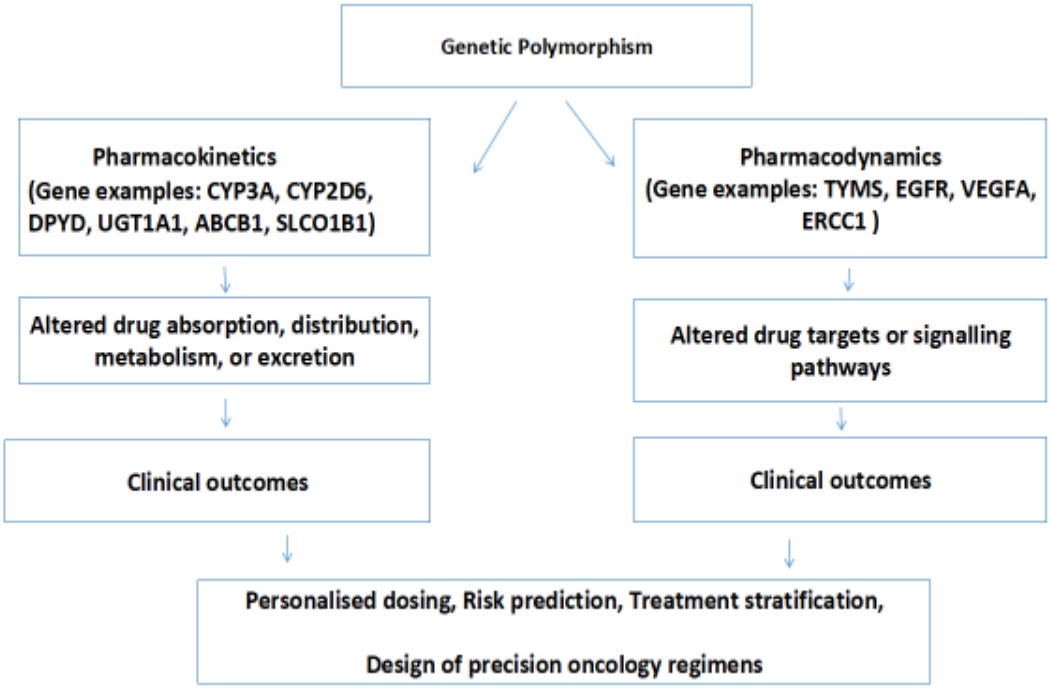

Fig. 1.The impact of genetic polymorphisms on drug safety and efficacy in cancer therapy

This narrative review aims to highlight novel genetic markers and their potential applications in chemotherapy, hormonal therapy, targeted therapy, and monoclonal antibody therapies within clinical practice. By summarising recent findings, we examine how these markers influence PKs, therapeutic response, resistance, and toxicity. We also highlight how PGx insights can guide personalised treatment to improve outcomes and reduce AEs.

2. MATERIAL AND METHODS

2.1. Sources of Information

Peer-reviewed scientific studies were collected using scholarly databases such as PubMed, Scopus, Google Scholar, Web of science, ScienceDirect, and Elsevier from December 2024 to March 2025. Research published between 2020 and 2025 was included to capture recent developments in the field. Additionally, reference lists of relevant reports were examined to enhance the selection.

2.2. Search Terms

Reviewers carried out independent manual searches. To gather relevant information, search terms such as “Pharmacogenetics”, “Pharmacogenomics”, “Pharmacokinetic”, “Cancer treatment”, “Gene expression”, “Genetic polymorphism”, “Chemotherapy”, and “Personalised medicine”, along with key words relevant to our study were used. Inclusion was limited to original, peer-reviewed studies of high quality published in English, with the exception of a single Ukrainian-language article accompanied by an English abstract. Eligible studies investigated associations between gene polymorphisms in DMEs or transporter proteins and therapeutic agents used in oncology. The selection encompassed case–control studies, *in vitro* investigations,

regulatory agency reports, case reports, meta-analysis, narrative reviews, as well as retrospective, prospective, and observational studies addressing the integration of genetic polymorphisms into cancer treatment. Exclusion criteria comprised outdated data, irrelevant topics, study protocols, and letters to the editor.

2.3. Assessment of Bias Risk in the Included Literature

The risk of bias in the included studies and reviews may affect the overall reliability and interpretability of the findings presented in this review.

3. RESULTS

3.1. Study Selection Process

The results of the search process are presented in Fig. 2. Initially, 1252 papers were identified, followed by the removal of 920 duplicates. Eligibility screening further reduced the records to 388. Ultimately, 41 articles met the inclusion criteria for this review [8]. A thorough analysis of the selected studies was conducted, with a focus on the potential of PGx testing and the development of novel biomarkers to optimise systemic cancer therapy.

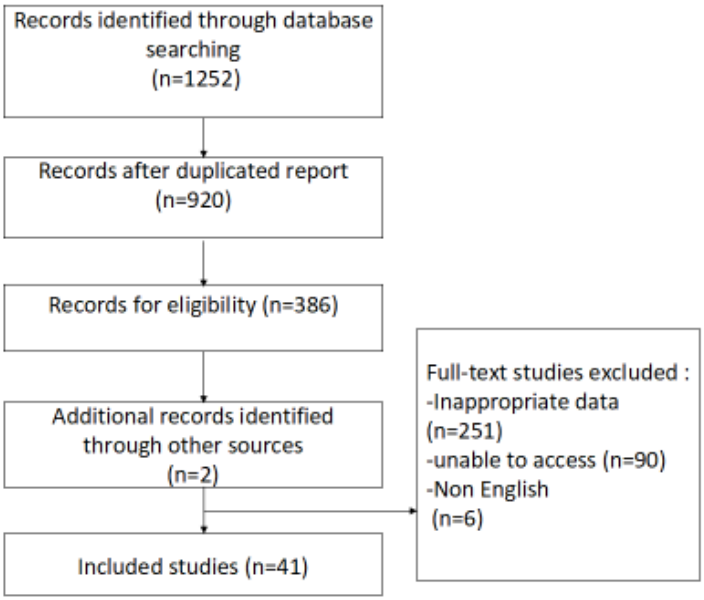

Fig. 2. Flow chart for the literature selection process

4. DISCUSSION

4.1. Integration of Genetic Polymorphisms in Drug-Metabolising Enzymes with Treatment Outcomes in Cancer Therapy

Metabolising enzymes convert xenobiotics, including drugs, into metabolites that reflect their safety and toxicity. Factors like age, gender, diet, gut flora, stress, and genetic polymorphisms influence these enzymes' function, affecting drug PKs and leading to varied therapeutic outcomes [9, 10, 11].

4.1.1. Impact of Cytochrome P450 Polymorphisms on the Safety and Efficacy of Systemic Cancer Therapy

This section highlights key cytochrome P450 (CYP) gene variants that influence the PKs of widely used anticancer agents, with a focus on recent clinically relevant findings.

Tyrosine kinase inhibitors

The CYP3A subfamily, particularly CYP3A4 and CYP3A5, plays a central role in metabolising 30–50% of drugs, including many anticancer agents, and is notable for its high polymorphism and hepatic expression [12, 13].

Tyrosine kinase inhibitors (TKIs), approved for the treatment of chronic myeloid leukaemia (CML) [14], are primarily metabolised by the CYP3A4 and CYP3A5 enzymes. Consequently, PGx variations in these enzymes may enhance or reduce their activity, altering the metabolism rate (MR) of these drugs and influencing DDIs during co-administration [15]. Although imatinib was the pioneering TKI approved for treating CML and gastrointestinal stromal tumours [16], treatment discontinuation due to suboptimal response or side effects remains a challenge [14]. Building on these findings, Chen et al. [16] recently conducted an *in vivo* study investigating the impact of CYP3A4 genetic polymorphisms on imatinib metabolism by expressing recombinant human CYP3A4 enzymes in insect microsomes and analysing metabolic activity using liquid chromatography-tandem mass spectrometry. *CYP3A4*14* was found to exhibit a higher MR (2.284 ± 0.168, $p < 0.001$), suggesting an extensive metaboliser phenotype potentially linked to reduced drug efficacy. Conversely, *CYP3A41* and *CYP3A4*18* variants showed reduced affinity for imatinib metabolism during co-administration with azole antifungals, increasing toxicity risk [16].These findings underscore the clinical relevance of PGx testing to personalise treatment. It is proposed that combining genotyping with careful monitoring of concomitant medications can optimise TKI dosing and reduce adverse effects, advancing personalised cancer therapy. Furthermore, the similar metabolic activity of *CYP3A4* variants toward both imatinib and cabozantinib suggests potential for developing unified PGx-guided dosing algorithms across multiple TKIs [16].

Polymorphisms in DMEs and membrane transporters influence PK processes, thereby altering drug exposure-response and exposure-toxicity relationships [17]. In this context, Van Eerden et al. conducted a non-inferiority trial, assessing 207 cancer patients carrying the *CYP3A4*22* allele, who received a 20–30% reduced dose of various TKIs. The trial compared treatment efficacy with that of wild-type patients who were administered standard doses, as recommended in the Summary of Product Characteristics by the European Medicines Agency. Interestingly, although *CYP3A4*22* carriers did not demonstrate non-inferior systemic exposure compared to wild-type patients—particularly for imatinib—the incidence of grade ≥ 3 AEs remained similar between groups [18]. Accordingly, while a 2023 international consensus by key PGx organisations—such as the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium (CPIC), and Dutch Pharmacogenetics Working Group (DPWG)—has recognised the relevance of standardised *CYP3A4* and *CYP3A5* genotyping in clinical practice, it is not yet intended to inform direct dosing decisions [19].

Platinum-based anticancer drugs

Platinum-based anticancer drugs, including cisplatin, carboplatin, and oxaliplatin, are widely used in the chemotherapy of various malignancies, such as breast, ovarian, and colorectal cancers.

However, systemic toxicities, including hepatotoxicity, nephrotoxicity, neurotoxicity and ototoxicity, as well as chemoresistance, remain major limitations of use for these drugs [20-22]. Genetic polymorphisms play a crucial role in these processes, and their incorporation into clinical practice may provide valuable predictive indicators of treatment response and patient outcomes [23]. This relevance is reflected in a genotyping assessment of 262 oesophageal cancer patients undergoing platinum-based treatment, which demonstrated that the *CYP3A5* rs776746 CT genotype was modestly associated with an increased risk of severe myelosuppression (OR = 1.96, 95% CI = 1.12–3.42, p = 0.019). Moreover, in patients treated with nedaplatin, this variant was significantly associated with higher odds of leukopenia (OR = 3.03, 95% CI = 1.17–7.86, p = 0.023) and neutropenia (OR = 3.28, 95% CI = 1.13–9.57, p = 0.030) [24]. These findings raise the possibility that the *CYP3A5* rs776746 polymorphism could serve as a predictive marker for haematological toxicity, particularly in nedaplatin-treated patients. Incorporating such information into risk assessment strategies may help individualise therapy, reduce the risk of severe adverse effects, and improve the tolerability of platinum-based regimens. Further studies are warranted to confirm these associations and support their translation into clinical practice.

Currently, the associations between CYP polymorphisms, chemotherapy response, and survival in patients receiving platinum-based treatment have garnered significant research attention [25]. Genotyping of drug-metaboliser-related genes in 230 patients with high-stage, high-grade epithelial ovarian cancer receiving platinum-based treatment revealed a significant association between the *CYP3A4* rs2740574 G allele and an increased risk of disease progression and chemoresistance, as evidenced by reduced progression-free survival (HR: 2.03, 95% CI: 1.38–3.96, p = 0.0016) and a shorter platinum-free interval (HR: 2.47, 95% CI: 1.46–4.20, p = 0.0008) [26]. These findings are further supported by a recent review by Al-Saraireh et al. [27], which highlights the impact of CYP polymorphisms on the metabolism of chemotherapeutic agents in ovarian cancer.

Tamoxifen

Tamoxifen, the first targeted cancer therapy, is widely used in breast cancer treatment and prevention. Its effectiveness can be influenced by genetic polymorphisms in metabolic enzymes, particularly the highly polymorphic CYP2D6, which is crucial for tamoxifen metabolism [28, 29, 30]. To harmonise the results of *CYP2D6* genotype translation to metaboliser phenotype across different guidelines, experts have updated the translation [31]. However, the association between *CYP2D6* genotypes and tamoxifen therapy for breast cancer remains a subject of debate [32]. Assessment of *CYP2D6* genotypes in 1,309 women diagnosed with stage I–III breast cancer and receiving tamoxifen in Sweden revealed a higher mortality rate in ultrarapid metabolisers (UM) (HR = 4.52, 95% CI: 1.42–14.37) and poor metabolisers (PMs) (HR = 2.59, 95% CI: 1.01–6.67). Additionally, 18.8% of UM patients discontinued tamoxifen within the first six months of treatment, a factor that may have contributed to the increased mortality [33]. Similar results regarding six-month

tamoxifen discontinuation were reported in the KARISMA dose determination trial, where the rate was 44.4% higher for UMs. This has been attributed to elevated levels of the active metabolite endoxifen, which can lead to excessive adverse effects and subsequent treatment discontinuation [34]. Investigation of inter-ethnic differences in CYP2D6 activity suggests that genotype–phenotype relationships are largely driven by allele frequency variations across ethnic groups [35]. This hypothesis is supported by an investigation involving 229 women with breast cancer receiving tamoxifen, who participated in the South African Breast Cancer Health Outcomes Study (SABCHO). The study identified *CYP2D6*17* and **29* as the most prevalent alleles (21% and 7.9%), both linked to reduced enzyme activity, lower endoxifen concentrations, and higher MR [N-desmethyltamoxifen/endoxifen], indicating diminished efficacy [36]. However, in 140 Iraqi women with breast cancer treated with tamoxifen, *CYP2D6*4, *10,* and **41* were associated with disease recurrence. *CYP2D6*41* was the most prevalent reduced-function allele (68.67%) in the recurrence group, associated with poorer prognosis and shorter recurrence-free survival [37]. Further supporting the role of inter-ethnic variability, a study in Algerian oestrogen receptor-positive breast cancer patients found that carriers of *CYP2D6*10, *17, *41*, or*5/*5*, classified as intermediate metabolisers or PMs, exhibited significantly lower plasma endoxifen levels, and various stages of relapse compared with *CYP2D6*1* normal metabolisers ($p < 0.05$) [38] . These findings highlight the clinical relevance of ethnic-specific allele distributions in tamoxifen PGx.

While some studies have reported an association between *CYP2D6* alleles and tamoxifen response, others have not, leading to inconsistent clinical recommendations. In line with this variability, although *CYP2D6*41* was identified as the most frequent allele (9.28%) among 95 female patients with stage I–III breast cancer receiving tamoxifen therapy, no significant differences were observed in the distribution of CYP2D6 phenotypes between patients with and without recurrence, nor in the incidence of hot flashes [39].

A comprehensive understanding of DDIs is crucial for optimising treatment outcomes. For instance, the administration of CYP2D6 inhibitors to mitigate tamoxifen side effects may lower plasma endoxifen levels and reduce efficacy [40]. However, efavirenz did not increase endoxifen levels or cause significant interactions in the study by Chiwambutsa et al. [36]. Genotyping facilitates identification of pharmacogene variants, including those encoding DMEs and transporters, which influence drug metabolism and therapeutic response [41]. Table 1 summarises the association between CYP gene polymorphisms and responses to various cancer therapies.

Table 1. Association between *CYP* Gene Polymorphisms and Response to Cancer Treatment

Anticancer agents	CYP subfamilies	*CYP* allelic variants/SNPs/phenotypes	Therapeutic responses	References
Imatinib	CYP3A4	*CYP3A4*14*	Reduced efficacy	[16]
Imatinib+ketoconazole, itraconazole, fluconazole		*CYP3A4*1* and **18*	Increased the risk of imatinib toxicity	[16]
TKIs		*CYP3A4*22*	No changes in drug toxicity after dose reduction	[18]
Nedaplatin		rs776746 CT	Increased the risk of toxicity	[24]
Platinum-based treatment		rs2740574, and the G allele	Increased risk of disease progression and chemoresistance	[26]
Tamoxifen	CYP2D6	UMs and PMs	Increased mortality rate	[33, 34]
		*CYP2D6*17* and **29*	Reduced drug efficacy	[36]
		*CYP2D6*4*, **10*, and **41*		[37]
		*CYP2D6*10*,**17*,**41*, or **5/*5*	Associated with various stages of relapse	[38]
		*CYP2D6*41*	No association with differences in drug safety and efficacy	[39]

*Abbreviations are available in the main text

4.1.2. Genetic Variability in Non-P450 Metabolising Enzymes and Its Clinical Implications

4.1.2.1. Glutathione S-transferases

Glutathione S-transferases (GSTs), a major class of phase II detoxification enzymes, contribute to the biotransformation of xenobiotics and therapeutic agents. They are also implicated in cellular signalling pathways and the development of drug resistance. Human cytosolic GSTs, encoded by genes in the alpha (A), mu (M), omega (O), pi (P), sigma (S), theta (T), and zeta (Z) subfamilies, exhibit considerable polymorphism [42-44]. Polymorphisms in the *GSTP1* gene may result in the expression of proteins with reduced detoxifying enzyme activity, leading to drug accumulation that can either increase the risk of toxicity or enhance therapeutic efficacy [45]. In patients with colorectal cancer, the presence of the *GSTP1 c.313A>G* polymorphism was associated with several acute platinum-induced toxicities, including vomiting (p = 0.042) and skin ulceration (p = 0.018). A higher incidence of severe vomiting was also observed in patients carrying AG and

GG genotypes (66.7% and 100%, respectively; $p = 0.027$) [46]. However, in a recent study, Nairuz et al. reported no significant association between the *GSTM1* and *GSTT1* null genotypes and platinum-induced haematological and gastrointestinal toxicities in Bangladeshi patients with lung cancer [47]. These contrasting findings across cancer types and ethnic populations underscore the complexity of GST-related PGx and highlight the need for context-specific interpretation.

Nevertheless, among women with breast cancer receiving doxorubicin (Adriamycin), the *GSTT1* null genotype was associated with mild neutropenia (OR = 2.84, 95% CI: 1.06–7.56) and severe nausea and vomiting (OR = 3.75, 95% CI: 1.46–9.59). Similarly, the *GSTP1* rs1695 AG and GG genotypes were correlated with an increased risk of mild mucositis, with odds ratios of 3.48 and 3.22, respectively [48]. In ovarian cancer patients undergoing carboplatin/paclitaxel-based chemotherapy, the *GSTP1* c.313A>G variant was linked with haematological toxicity. Patients with the AA genotype predominantly experienced grade 0-2 anemia compared to those with AG and GG variants ($p = 0.04$), and did not experience thrombocytopenia ($p < 0.01$) [49]. These findings are further supported by a systematic review and meta-analysis by Kim et al., which confirmed a significant association between the *GSTP1* rs1695 and platinum-induced toxicities. Notably, while some studies indicated a protective effect of the variant against gastrointestinal toxicity, others identified it as a risk factor for haematological toxicity and neutropenia [50]. Chen et al. also reported a significant association between the *GSTP1* rs1695 GG genotype and severe leukopenia (OR = 6.21; 95% CI: 1.07–36.00, $p = 0.042$, FDR = 0.100), although the wide confidence interval warrants cautious interpretation [24]. Beyond toxicity, *GSTP1* polymorphisms appear to influence therapeutic response. In patients with bladder cancer treated with gemcitabine plus cisplatin, the 313G allele was more frequent among responders ($p = 0.015$), and AG/GG carriers were more likely to benefit compared with AA carriers (OR = 3.05, 95% CI: 1.05–8.84) [51]. Conversely, in non-small cell lung cancer (NSCLC), the *GSTP1* rs1695 AA genotype was associated with longer progression-free survival (9.5 vs. 5.6 months, $p = 0.007$) and overall survival (22.0 vs. 16.6 months, $p = 0 .003$) in patients receiving bevacizumab-based therapy [52]. Another study in NSCLC supported this variant as a predictive marker for severe neutropenia ($p = 0.044$) and heightened sensitivity to platinum-based chemotherapy [53]. Collectively, these findings underscore the complex and context-dependent role of *GSTP1* polymorphisms in modulating chemotherapy response and toxicity. Moreover, evidence linking *GSTP1* genetic variants to increased cancer risk [42] highlights their potential relevance for the development of targeted anticancer strategies. Table 2 summarises the association between *GSTP1* Gene polymorphisms and responses to various cancer therapies.

Table 2. Association between *GSTP1* Gene Polymorphisms and Cancer Treatment Response

Gene polymorphisms/Genotypes	Anticancer agents	Therapeutic responses	References
*GSTP1*c.313A>G *(*AG and GG genotypes*)*	Platinum-based	Increasedrisk of drug toxicity	[46]
GSTM1 and *GSTT1* null genothypes	Platinum-based	No association with drug toxicity	[47]
GSTT1 null genotype, *GSTP1* rs1695 AG and GG genotypes	Doxorubicin (Adriamycin)	Associated with drug toxicity	[48]
GSTP1 rs1695 (c.313A>G), AA genotype	carboplatin/paclitaxel-based	Decreased severity of drug toxicity	[49]
GSTP1 rs1695	Platinum-based	Conflicting evidence regarding association with drug toxicity	[50]
GSTP1 rs1695, GG genotype	Platinum-based	Increased severity of drug toxicity	[24]
GSTP1 rs1695 (c.313A>G)AG or GG genotypes	Gemcitabine+cisplatin	Increased drug efficacy	[51]
GSTP1 rs1695, AA genotype	bevacizumab-based	Increased drug efficacy	[52]
GSTP1 rs1695	Platinum-based	Paradoxical effects: increased risk of toxicity and improved response	[53]

4.1.2.2. The uridine 5′-diphospho-glucuronosyltransferases

The uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT) enzyme superfamily—including the UGT1A, UGT2A, and UGT2B isoforms—is localised in the microsomal fraction of various tissues, with highest expression in the liver, where these enzymes catalyse conjugation reactions [54].

Irinotecan has been widely utilised in the treatment of advanced solid malignancies, such as colorectal cancer, gastric cancer, and small cell lung cancer, showing notable survival benefits, particularly in gastrointestinal tumors [55]. Recent reviews highlight clinically relevant *UGT1A1* biomarkers, particularly *UGT1A1*28* and *UGT1A7* in relation to irinotecan-induced toxicity, emphasising the role of PGx in individualising treatment and reducing severe AEs [55-57]. Yu et al., reported consistent associations between *UGT1A1*28* and *UGT1A1*6* polymorphisms and irinotecan toxicity in colorectal cancer [58]. Similarly, Zhu et al. found that *UGT1A1*6* significantly linked to neutropenia in both homozygous and heterozygous carriers [59]. Supporting this, a

study in Thai patients confirmed association of *UGT1A1*28* (OR = 2.7, 95% CI: 0.8–8.8; p = 0.087), and *UGT1A1*6* (OR = 12.5, 95% CI: 3.4–45.7; $p < 0.001$) with severe neutropenia [60]. Accordingly, DPWG recommends a 70% starting dose of irinotecan for patients who are *UGT1A1*28/*28* PMs, with dose escalation based on tolerance [61]. Complementing these data, a meta-analysis by Geng et al. showed that, while the *UGT1A*16* polymorphism was not associated with irinotecan efficacy, it was significantly correlated with the incidence of neutropenia and high-grade diarrhoea in patients receiving this chemotherapeutic agent [55]. Extending the investigation of *UGT1A* family variants to other therapeutics, giredestrant, a selective oestrogen receptor degrader used in the treatment of oestrogen receptor-positive breast cancer, is primarily metabolised by *UGT1A4*, as demonstrated by *in vitro* analyses. In this context, the *UGT1A42* and *UGT1A43* polymorphisms were not associated with any alterations in the drug's safety or efficacy [62]. The analysis of these results supports genotype-guided dosing recommendations, such as those from the DPWG. Furthermore, comparative analyses across drugs reveal variability in PGx impacts within the *UGT1A* family, underscoring the importance of drug-specific considerations in personalised therapy. The association of *UGT g*ene polymorphisms and cancer treatment response is summurised in Fig. 3.

4.1.2.3. Dihydropyrimidine DehydrogenasePolymorphisms and Fluoropyrimidine Toxicity

Fluoropyrimidines, including 5-fluorouracil (5-FU), capecitabine, and tegafur, are antimetabolic agents widely used as monotherapy or in combination regimens for the treatment of various malignancies. However, fluoropyrimidine-related toxicities, including mucositis, diarrhoea, nausea, vomiting, neutropenia [63], hand-foot syndrome, myelosuppression, and cardiotoxicity, are often associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD is the key enzyme, encoded by the *DPYD* gene, responsible for fluoropyrimidine metabolism [64, 65].

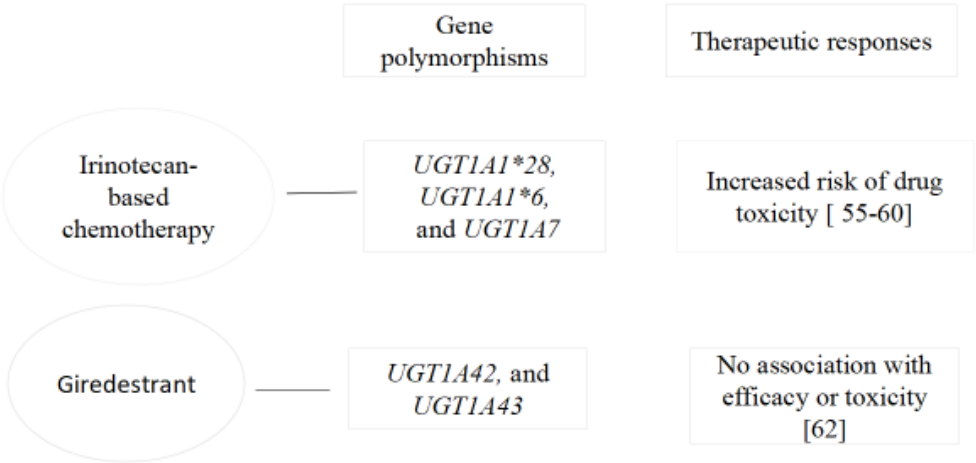

Fig. 3. The Impact of *UGT* Gene Polymorphisms on Cancer Treatment Response

A meta-analysis evaluating the relationship between *DPYD* polymorphisms and fluoropyrimidine-related treatment mortality identified *DPYD***2A* (rs3918290) as the most prevalent variant, followed by *DPYD***13* (rs55886062) and HapB3 (rs75017182). These variants were significantly associated with an increased risk of fluoropyrimidine-induced mortality (OR = 34.86, 95% CI: 13.96–87.05; $p < 0.000001$) [66]. Notably, these pathogenic variants, along with *DPYD D949V*, which are linked to DPD deficiency, have been strongly associated with an increased risk of severe toxicity from fluoropyrimidine chemotherapy [65, 67]. The Swiss Group of Pharmacogenomics and Personalised Therapy reported that 6.5% of the Swiss population carry one or more of the four *DPYD* variants: rs3918290, rs55886062, rs67376798, and the HapB3 haplotype (comprising rs75017182 and rs56038477). These individuals have a 40–50% risk of developing toxicity when treated with standard doses of fluoropyrimidines [68]. However, Turner et al. presented individuals who carry c.1236G>A (rs56038477), but not the c.1129-5923C>G (rs75017182) SNPs, indicating that these variants are not in perfect linkage disequilibrium. This suggests that the c.1236G>A variant may not be an accurate marker for *DPYD* genotyping to guide the dose adjustment of fluoropyrimidines, such as 5-FU and capecitabine, to prevent adverse effects [69]. This challenges the theory proposed by DPWG, which suggested that these variants were in complete linkage disequilibrium [65]. In this context, a study of 1,371 cancer patients treated with fluoropyrimidines found that a haplotype consisting of both c.85T>C and c.496A>G was linked to a higher risk of fluoropyrimidine toxicity (OR = 1.57, 95% CI: 1.15–2.13, $p = 0.0041$). This haplotype was identified in approximately 7.1% of cases. However, the c.496A>G variant alone was associated with a significantly increased likelihood of severe (grade ≥3) toxicity (OR = 1.38, 95% CI: 1.01–1.88, $p = 0.0405$) [70]. The observation of the frequency of *DPYD* variants in cancer patients from different populations may provide valuable insights for oncologists in selecting appropriate fluoropyrimidine-based chemotherapy. For example, results from the PhotoDPYD study conducted in Spain revealed that nearly 5% of patients with cancer were carriers of at least one defective *DPYD* variant. Among these, the most frequently identified variant was c.1129-5923C>G (rs75017182), with 2.9% of patients being heterozygous and only 0.09% homozygous [71]. However, the association between *DPYD* heterozygosity and an increased risk of severe toxicity induced by fluoropyrimidine chemotherapy remains controversial. A 56-year-old Caucasian male, heterozygous for the common *DPYD* c.2846A>T variant and the rare c.2872A>G variant—both classified as loss-of-function—was reported to have experienced severe 5-FU-related toxicity [72]. In contrast, a 48-year-old Caucasian male with left-sided colon adenocarcinoma, compound heterozygous for *DPYD* (HapB3 and c.2194G>A), received pharmacogenetically guided capecitabine adjuvant therapy with a 25% dose reduction. Despite early low-grade toxicity, the patient showed no evidence of disease at the 6-month follow-up [73]. These contrasting case reports illustrate the clinical complexity of managing *DPYD* heterozygosity. While some carriers experience severe toxicity despite carrying only one identified loss-of-function allele, others may tolerate fluoropyrimidine therapy when guided by PGx-informed dose adjustment. Supporting this approach, a genotyping study of 370 patients with various

gastrointestinal cancers revealed that 33 (8.8%) were heterozygous for *DPYD* variants. The authors proposed that a 25%–50% dose reduction in fluoropyrimidines could reduce the risk of high-grade toxicity in these patients. This hypothesis was supported by the absence of statistically significant differences in the incidence of grade ≥3 adverse events between heterozygous *DPYD* variant carriers and wild-type individuals [74]. These consistent findings align with recent regulatory guidance. The FDA's 2024 labeling update for FU now includes PGx content advising consideration of DPYD testing prior to treatment [75]. Similarly, CPIC's updated 2024 guideline recommends a 50% dose reduction for DPYD IMs (activity score 1–1.5), including HapB3 carriers, with subsequent dose titration based on tolerance and therapeutic monitoring [76]. The discovery of new *DPYD* variants associated with fluoropyrimidine-related toxicity is crucial for improving personalised cancer treatment. After analysing *DPYD* polymorphisms IVS14+1G>A, 2846A>T, and 2194G>A in 73 patients with colorectal cancer, IVS14+1G>A was identified as the most prevalent variant with a frequency of 5.5%. However, the incidence of adverse effects associated with various fluoropyrimidine-based regimens, including diarrhoea, nausea, vomiting, mucositis, peripheral neuropathy, and hair loss, was not significantly influenced by these *DPYD* polymorphisms [77]. In this context, an evaluation of *DPYD* genetic polymorphisms in 75 Thai patients with colorectal cancer receiving various 5-FU-based chemotherapy regimens revealed a significant association between the *DPYD*9A (85A>G)* variant and reduced enzyme activity. This was evidenced by its strong correlation with leukopenia ($p < 0.001$) and high-grade thrombocytopenia ($p < 0.001$). Notably, the homozygous GG genotype of *DPYD*9A* was strongly associated with severe neutropenia [55]. Similarly, Varma et al. reported that colorectal cancer patients of South Indian origin carrying the *DPYD*9A* GG genotype exhibited significantly higher plasma 5-FU levels three hours after receiving capecitabine, suggesting impaired drug metabolism [78]. These findings underscore the clinical importance of identifying *DPYD*9A* homozygosity as a predictor of fluoropyrimidine-related toxicity across different populations. The impact of *DPYD* gene polymorphisms on therapeutic response in cancer is outlined in Table 3.

4.2. Integration of Gene Polymorphisms in Membrane Protein Transporters into Chemotherapy Safety and Efficacy

Membrane transporter proteins, such as adenosine triphosphate-binding cassette (ABC) transporters, including ABCB, ABCC, and ABCG, which mediate drug efflux, and solute carrier (SLC) transporters, primarily responsible for drug influx, play a crucial role in the response to anti-cancer drugs [79, 80]. Multidrug resistance (MDR) represents a major obstacle in chemotherapy, as it involves diverse cellular mechanisms that enable tumour cells to evade the cytotoxic effects of anticancer agents with varying structures and mechanisms of action. Elucidating the molecular basis of MDR, including the roles of specific genes regulating the expression of P-glycoprotein (P-gp) and multidrug resistance-associated proteins, is essential for understanding the complexity of drug resistance. This knowledge may facilitate the development and application of more effective and selective P-gp inhibitors, enhancing chemotherapy efficacy [81, 82].

Table 3. Association of *DPYD* Gene Polymorphisms with Fluoropyrimidine Therapeutic Response

Gene polymorphisms	Therapeutic responses	References
*DPYD*2A* (rs3918290), *DPYD*13* (rs55886062), HapB3 (rs75017182), *DPYD* rs67376798, and *DPYD D949V*	Increased risk of severe drug toxicity and mortality	[66-68]
HapB3 (rs56038477)	Controversial association with increased risk of severe drug toxicity	[69]
Haplotypes (c.85T>C and c.496A>G)	Severe drug toxicity	[69]
DPYD c.2846A>T and c.2872A>G variants	Increased risk of severe 5-FU-related toxicity	[72]
DPYD variants (HapB3 and c.2194G>A)	Associated with low-grade capecitabine toxicity	[73]
IVS14+1G>A, 2846A>T, and 2194G>A variants	No significant association with drug toxicity	[77]
*DPYD*9A* (85A>G), GG genotype	Associated with an increased risk of severe 5-FU-related toxicity	[78]

*Abbreviations are available in the main text

Tyrosine kinase inhibitors

The potential relationship between polymorphisms in genes encoding membrane proteins and the response to TKIs chemotherapy in various cancers has garnered the interest of researchers. SNP genotyping in the *ABCB1* and *ABCG2* genes in patients with chronic myelogenous leukaemia receiving dasatinib as second- or third-line therapy revealed significant associations with AEs and survival outcomes. The *ABCB1* rs7787082 genotype was significantly associated with a higher risk of severe haematological adverse events (OR = 4.46, 95% CI = 1.38–14.39, p = 0.012), while *ABCG2* rs2725256 was linked to non-haematological complications (OR = 4.71, 95% CI = 1.20–18.47, p = 0.026). Three *ABCB1* polymorphisms—rs3842, rs2235023, and rs22114102—were significantly associated with survival outcomes. Specifically, rs3842 (HR = 1.84, 95% CI = 1.01–3.33, p = 0.012) and rs2235023 (HR = 2.28, 95% CI = 1.03–5.02, p = 0.027) were correlated with overall survival under the codominant model. In addition, rs2235023 (HR = 2.49, 95% CI = 1.13–5.50, p = 0.011) and rs22114102 (HR = 1.90, 95% CI = 1.00–3.63, p = 0.020) were significantly associated with progression-free survival [83]. Gómez et al., in a recent review and meta-analysis, concluded that polymorphisms in the *ABCB1* and *SLCO1A2* transporter genes are associated with imatinib treatment outcomes. Specifically, the *ABCB1* 1236CC genotype was correlated with an increased risk of cytogenetic relapse, while the *SLCO1A2* 361GA variant was associated with complete molecular response [84]. These findings highlight the relevance of transporter gene polymorphisms as predictive biomarkers for both the efficacy and safety of TKI therapy, providing novel evidence that supports the

integration of PGx profiling into personalised cancer treatment strategies. The association between membrane transporter gene polymorphisms and response to tyrosine kinase inhibitors is presented in Table 4.

Platinum-based chemotherapy

To evaluate the response to platinum-based chemotherapy, an investigation involving 230 patients with high-stage, high-grade epithelial ovarian cancer treated with this regimen found that the *ABCG2* rs3219191 variant was associated with a reduced risk of death (HR = 0.77, 95% CI: 0.60–0.98, p = 0.036), disease progression (HR = 0.77, 95% CI: 0.62–0.97, p = 0.0251), and platinum resistance (HR = 0.74, 95% CI: 0.59–0.93, p = 0.0091) [26]. These findings elucidate the association between the *ABCG2* polymorphism and intracellular drug accumulation, thereby highlighting its potential role in mediating drug resistance.

Table 4. The Effect of Membrane Transporter Gene Polymorphisms on Response to Tyrosine Kinase Inhibitors

Anticancer agents	Gene Polymorphisms	Therapeutic Responses
Dasatinib [83]	*ABCB1* rs7787082, *ABCG2* rs2725256	Increased risk of drug severe toxicity
	ABCB1 rs3842, rs2235023, and rs22114102	Favourable survival outcome
Imatinib [84]	*ABCB1* 1236CC	Decreased efficacy of the treatment
	SLCO1A2 361GA	Significant positive outcome

Furthermore, reduced expression of genes encoding the protein constituents of these pumps (*SLC31A1/CTR1*, *SLC22A1/OCT1*, *SLC22A2/OCT2*, and *SLC22A3/OCT3*) can lead to platinum resistance [79]. Wang et al. uncovered that the PGx interaction between platinum uptake (*SLC31A1*) and efflux (*ABCG2*) transporter genes in stage III-IV non-small cell lung cancer patients receiving platinum-based doublet chemotherapy may be associated with survival outcomes. This hypothesis was validated by the combined effect of *SLC31A1* rs10759637 and *ABCG2* (rs4148157, p interaction = 0.03; rs2231142, p interaction = 0.007) on overall survival [80]. Worth noting, in addition to protein transporters, there are complex factors and regulatory genes involved in the platinum resistance mechanism, which have been comprehensively reviewed by Huang et al. [79]. The primary limitation in the clinical application of platinum-based therapies is the onset of toxicity, particularly haematologic complications such as myelosuppression, which may manifest as anaemia, leukopenia, neutropenia, or thrombocytopenia [85]. SNP analysis by Cheng et al. revealed that the *ABCB1* rs1045642 AA genotype was a significant risk factor for severe leukopenia (OR = 5.83, 95% CI: 1.63–20.83, p = 0.007)

[24]. However, analysis of multiple studies found no significant association between the *ABCB1* G2677T/A polymorphism and platinum-induced grade III–IV overall, haematological, or gastrointestinal toxicities [86]. In contrast, a PGx investigation on 239 patients with oesophageal cancer receiving platinum-based therapy plus 5-FU identified the *ABCC2* -24C/T + T/T genotypes as significant predictors (P = 0.038) of high-grade haematological toxicity, as well as risk factors for it (p = 0.036) [87]. Further supporting these associations, in a genomic study of patients with oesophageal cancer treated with docetaxel, cisplatin, and 5-FU, Nomura et al. identified significant associations between the *ABCB1* 3435C>T and ABCC2 +9383C>G polymorphisms and the risk of severe neutropenia: OR = 2.19 (95% CI: 1.09–4.42, p = 0.028) and OR = 2.34 (95% CI: 1.11–4.95, p = 0.026), respectively [88]. Extending this line of evidence, genotyping analysis of 407 lung cancer patients undergoing platinum-based doublet chemotherapy showed that the heterozygous (GA) genotype of *ABCC1* (c.3173G>A) increased the risk of leukopenia (OR = 1.88, p = 0.04), while the *ABCC2* (c.4544G>A) GA variant was linked to a higher risk of anemia (AOR = 5.63, p = 0.03) [89]. Complementing these findings, Ferracini et al. reported that carriers of the *ABCB1* c.3435C>T variant had an elevated risk of developing grade II-III neurotoxicity (OR = 3.61, 95% CI: 1.08-121.01, p = 0.03), particularly among individuals with the CC and CT genotypes [49]. Moreover, in the study conducted by Sharma et al., patients carrying the heterozygous genotype of *ABCC1* (c.3173G>A) and *ABCB1* (c.1236C>T) exhibited an elevated risk of hepatotoxicity, with odds ratios of 2.06 (p = 0.02) and 1.85 (p = 0.01), respectively. Additionally, an increased risk of diarrhoea was observed in the heterozygous (GA) genotype of the *ABCC1* G3173A polymorphism (AOR = 2.78, p = 0.04) [89]. However, Sahoo et al. identified significant associations between *ABCC2* rs2804398 (P = 0.008), *ABCC1* rs9332430 (p = 0.01), and *ABCC4* rs943288 and the occurrence of gastrointestinal AEs. Notably, for rs943288, both the heterozygous and homozygous mutant genotypes conferred elevated risks, with odds ratios of 2.72 (95% CI: 1.306–3.954, p = 0.004) and 9.11 (95% CI: 1.675–49.57, p = 0.011), respectively [90]. These findings highlight the relationship between novel ABC family gene variants and AEs associated with platinum-based chemotherapy, underscoring the importance of incorporating genotype and zygosity into PGx screening to improve the safety of this regimen. Table 5 presents the influence of membrane transporter gene polymorphisms on the response to platinum-based chemotherapy.

Table 5. The Impact of Membrane Transporter Gene Polymorphisms on Response to Platinum-Based Chemotherapy

Gene polymorphisms	Therapeutic responses	Gene polymorphisms	Therapeutic responses
ABCG2 rs3219191	Improved drug efficacy [26]	*ABCB1* G2677T/A	No association with sever drug toxicity [86]
SLC31A1 rs10759637 and *ABCG2* (rs4148157, rs2231142) interaction	improved treatment outcomes [80]	*ABCC2* -24C/T + T/T genotypes	Increased risk of sever drug toxicity [87]
ABCB1 rs1045642 AA genotype	Increased risk of sever drug toxicity [24]	*ABCB1* 3435C>T and *ABCC2* +9383C>G	Increased risk of sever drug toxicity [49, 88]
ABCC1 (c.3173G>A), *ABCB1* (c.1236C>T)	Increased risk of sever drug toxicity [89]	*ABCC2* rs2804398, *ABCC1* rs9332430, and *ABCC4* rs943288	Increased risk of drug toxicity [90]

5. Perspective for using Pharmacogenetics and Oncology

Given the narrow therapeutic range and high toxicity potential of most anticancer agents, PGx is gaining increasing importance in oncology. This shift is further supported by advancements in DNA-genome sequencing and artificial intelligence-based drug selection technologies. These innovations enhance the detection of clinically significant genetic variants, enabling more precise and individualised treatment decisions and improving patient care. PGx is transforming oncology clinical trials by facilitating tumour DNA sequencing in non-responsive patients to uncover mechanisms of treatment failure. This targeted approach may reduce the need for large trial populations, as more specific data improves outcome interpretation [91]. Although initially focused on optimising chemotherapy, PGx applications now extend to immunotherapy and molecularly targeted therapies. Moreover, gene variants associated with tumour biology may provide prognostic information, guiding treatment decisions based on disease progression. Looking ahead, the successful implementation of PGx will depend on overcoming several persistent challenges, including limited accessibility, a shortage of trained specialists, high testing costs—particularly in low- and middle-income countries—and the lack of comprehensive data on global genetic diversity [92]. Therefore, the establishment of reliable strategies by health authorities to facilitate the integration of PGx into clinical practice is imperative.

Study limitations

This narrative review aimed to highlight recent research on genetic polymorphisms and their relevance to various cancer therapies. However, several limitations should be acknowledged. Due to constraints in page count and reference limits established by the journal, the review focused on selected drug classes and included only the most commonly prescribed agents within each category. In

addition, the discussion was limited to a subset of DMEs and membrane transporters. Several clinically significant genes involved in tumour biology, immune regulation, and intracellular signalling pathways were not explored in detail. For example, polymorphisms in *EGFR*, *PD-L1*, *KRAS*, *BRAF*, *TP53*, and *HER2* genes, involving pharmacodynamic mechanisms, have also essential PGx implications that were not addressed in this review. The primary aim of our review was to provide a comprehensive mechanistic overview of how gene polymorphisms affect the PKs of key anticancer drugs across multiple cancer types. We acknowledge the importance of targeted reviews and recommend conducting cancer type- or drug class-specific investigations to build upon the general insights presented here.

CONCLUSION

Polymorphisms in key genes—*CYP3A4/5*, *CYP2D6*, *GSTP1*, *UGT1A*, *DPYD*, and ABC transporters—significantly influence the metabolism, efficacy, and toxicity of various anticancer therapies, including TKIs, tamoxifen, platinum-based agents, irinotecan, and fluoropyrimidines. Emerging markers within these variants help predict clinical outcomes and guide dose adjustments. Integrating genotyping and zygosity in PGx improves personalised dosing and toxicity management. Despite evolving guidelines and variability by ethnicity and cancer type, comprehensive PGx profiling is vital to optimise outcomes and reduce adverse effects. Progress in PGx offers more tailored oncology care, but overcoming challenges like access, cost, training, and data gaps requires strong health authority support.

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تحسين العلاج الجهازي في الأورام: خطوة متقدمة في تطبيق علم الوراثة الدوائية – مراجعة سردية

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الملخص

يُعد توضيح الديناميكا الدوائية لعوامل مكافحة السرطان أمرًا أساسيًا لتحسين سلامتها وفعاليتها العلاجية .يوفر علم الوراثة الدوائية وعلم الجينوم الدوائي إطارًا لفهم التفاوت الفردي في استجابة الدواء وتقليل الآثار الجانبية من خلال تحليل المتغيرات الجينية التي تؤثر على إنزيمات استقلاب الدواء وناقلات الغشاء .في مجال الأورام، حيث تُعد السلامة والفعالية أمرين حاسمين، يكتسب العلاج الموجه شخصيًا، المستند إلى مؤشرات علم الوراثة الدوائية والتوصيات السريرية، أهمية متزايدة. يرتبط متغيرات مثل *CYP3A4*14*، *1**، *18** و *ABCB1* 1236CC بانخفاض فعالية الإيماتينيب وارتفاع خطر السمية .وتم ربط أليل *CYP2D6*17*، *29**، *4**، *10**، و *41** بانخفاض فعالية التاموكسيفين، في حين ورد ذكر أليل *CYP2D6*17*، *41**، *10**، و *5/5** في مراحل مختلفة من الانتكاس. ارتبطت الأنماط الجينية (GG و AG) *GSTP1* rs1695 c.313A>G، (rs9332430 و *ABCC1* (c.3173G>A و (3435C>T و *ABCB1* (c.1236C>T و (rs2804398و+9383C>G و –24C/T) *ABCC2* ، بالإضافة إلى *ABCC4* rs943288، بزيادة السمية الناتجة عن العلاجات القائمة على البلاتين .كما أُشير إلى متغيرات *UGT1A1*28*، *6** و UGT1A7 كعوامل مرتبطة بالسمية المرتبطة بالإيرينوتيكان .بالإضافة إلى ذلك، ارتبطت متغيرات (rs3918290) *DPYD*2A*، *13** (rs55886062)، rs67376798، و (rs75017182) HapB3 ارتباطًا قويًا بالسموم الشديدة الناتجة عن الفلوروبيريميدينات وزيادة الوفيات المرتبطة بالعلاج .مع تطور أبحاث علم الوراثة الدوائية، سيصبح دمجها في الممارسة الروتينية لعلاج الأورام أمرًا ضروريًا لتحسين النتائج العلاجية ودعم نهج أكثر تخصيصًا لعلاج السرطان.

الكلمات الدالة: علم الوراثة الدوائية، علم الجينوم الدوائي، السرطان، العلاج الكيميائي.