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PHARMACOGENOMIC PROFILING OF ABCG2 VARIANTS AND THEIR ROLE IN ENHANCING ANTI-CANCER DRUG COMBINATIONS FOR COLORECTAL CANCER THERAPY: SEMANTIC REVIEW

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ABSTRACT

Indeed, colorectal cancer (CRC) is one of the most common causes of cancer-related mortality, and systemic therapy resistance is a major barrier to achieving meaningful therapeutic outcomes. Among the transporters known to contribute to MDR, the ATP-binding cassette sub-family G member 2 (ABCG2, BCRP) has been highlighted in this context, since it is known to control the intracellular concentration of irinotecan metabolites and various drugs with anticancer and/or therapeutic properties, while being linked to processes such as stemness, EMT, autophagy, and plasticity. To synthesize the available evidence on ABCG2 genetic variants, tumor expression, and ABCG2-linked resistance biology in CRC, with emphasis on whether pharmacogenomic profiling can improve anti-cancer drug combinations and patient selection. The study adopted a semi-systematic review methodology, following the PRISMA guidelines. PubMed, PubMed Central, and Google Scholar were used to obtain relevant studies published between January 2014 and March 2026. The studies were selected if they were written in English. Clinical, translational, prognostic, and preclinical studies that directly examined ABCG2 variants, ABCG2 expression, or ABCG2-mediated drug resistance in CRC were included. The studies were reviewed to contextualize implementation. The synthesis of the studies included a total of 50 studies after removing duplicates. The evidence converged on four main findings. First, the most common ABCG2 variant, rs2231142 (421C>A), showed a clinically meaningful association with irinotecan-induced toxicity, as the minor allele of the variant was associated with a decreased likelihood of severe adverse drug reactions in a real-world CRC patient cohort. Second, low ABCG2 expression in tumors, especially basolateral membranous ABCG2, correlated with a favorable objective response rate in first-line irinotecan-treated selected mCRC patient cohorts, whereas CSC-enriched or high ABCG2-overexpressing cell line models consistently showed increased drug efflux and resistance. Third, mechanistic evidence established ABCG2 as a core player in resistance mechanisms, which also include EGFR/MAPK, stemness, Golgi stress, EMT, and autophagy-related biology. Fourth, combination regimens using ABCG2 inhibitors, as well as upstream signaling pathway inhibitors, such as cetuximab, as well as experimental ABCG2 inhibitors dorsomorphin and tinodasertib, restored drug accumulation in drug-resistant CRC cell line models.

KEYWORDS: ABCG2, Colorectal Cancer, Pharmacogenomic Profiling, Multidrug Resistance, Irinotecan Response, Combination Therapy, Precision Oncology, Cancer Stem Cells.

1. INTRODUCTION

Pharmacogenomics has altered the treatment of patients with cancer, particularly those with colorectal cancer, as they will be treated according to their individual differences in how they metabolize, transport and respond to anticancer chemotherapy agents. Changing from a one-size-fits-all approach to one that considers how patients differ from each other is beneficial in determining which sequence of treatment works best, depending on their previous treatments, the adverse effects they have experienced from their previous treatments and the development of resistance. Pharmacogenomics has identified UGT1A1 as a significant genetic marker for predicting how patients will respond to irinotecan, however, the study of drug transporters has become very important in the development of potential strategies to combat drug resistance (Paulík et al. 2020, Reizine et al. 2020).

ABCG2 is a member of the ATP-binding cassette (ABC) superfamily of transmembrane transporters and encodes for the breast cancer resistance protein (BCRP), an efflux pump that transports drugs across membranes and can be found in numerous tissues, both normal and malignant. ABCG2 plays an important role in drug treatment for colorectal cancer as it can limit the amount of antitumour medications that can be accumulated within cancer cells. ABCG2 has been cited in relation to the pharmacokinetics and pharmacodynamics of irinotecan and its active metabolite SN-38, the biology of cancer stem cells, the metastatic potential of cancer cells and the development of adaptive resistance to both chemotherapy and targeted therapies (Palshof et al. 2020, Ozawa et al. 2021, Hao et al. 2023).

There is little cohesion among the existing literature examining ABCG2 in CRC. There are studies examining germline genetic variation of ABCG2, tumor tissue protein or transcript based expression, and laboratory models to test whether ABCG2 inhibition is able to resensitize previously resistant cells. This lack of cohesive evidence prevents a definitive understanding about whether ABCG2 is best considered exclusively an important pharmacogenetic marker, or an important biomarker of dynamic resistance to therapy, or as either of these as well as a valid therapeutic target. In addition, the introduction of three-dimensional tumor models, systems biology based approaches, and combination treatment strategies has increased the translational relevance of predicting ABCG2 response from a single marker based perspective (Sogawa et al., 2021; Gheytanchi et al., 2021; de Groot et al., 2025).

Therefore, this review will evaluate the current evidence at the intersection of pharmacogenomics and resistance biology. By evaluating ABCG2 genetic variation and ABCG2 expression as overlapping rather than discrete fields, the review will explore how inherited genetic variants, inducible expression of ABCG2, and pathway based regulation of ABCG2 together influence treatment outcomes. The review will also address the practical question: how can ABCG2 biological profiling improve treatment of CRC with currently available anti-cancer combination regimens, specifically with respect to irinotecan and overcoming multidrug resistant cancers?

1.1 Study Question

How do ABCG2 genetic variants and ABCG2-linked resistance pathways influence the effectiveness, toxicity, and optimization of anti-cancer drug combinations in colorectal cancer?

2. METHODOLOGY

Review design: Due to the varied study designs of the available literature, which included retrospective clinical studies, tissue-based studies, biomarker studies, mechanistic studies, and evidence review, a semi-systematic review design based on PRISMA guidelines was employed. The review was not prospectively registered, as the aim of the review was not meta-analysis but rigorous structured synthesis.

Databases and search strategy: Electronic searches were undertaken in PubMed and PubMed Central, and Google Scholar was also used as a supplementary resource due to its cross-disciplinary nature. The main search terms used were "ABCG2," "BCRP," "colorectal cancer," "colon cancer," "irinotecan," "SN-38," "pharmacogenomics," "polymorphism," "drug resistance," "combination therapy," "cetuximab," "cancer stem cells," "EMT," "autophagy," and

Eligibility criteria: The inclusion criteria for the study were that the research had to be peer reviewed, written in English, and focus on ABCG2 in CRC with relevance to drug response, toxicity, resistance, or treatment combination. The study design that met the inclusion criteria included clinical cohort studies, case-control genetic studies, translational biomarker research, and preclinical research using CRC cell lines. Narrative reviews were not included for analysis but were helpful for interpreting clinical translation. The study that did not meet the inclusion criteria included those that were unrelated to CRC, did not focus on ABCG2, were not related to drug response, had no relevance to treatment response, or were duplicates/commentary without extractable data.

Screening and data extraction: Titles and abstracts were screened first, followed by full-text eligibility review. Extracted variables included publication year, country/setting, design, population or model, ABCG2 domain studied (variant, expression, function, pathway interaction), treatment context, main numeric findings, and stated translational implication. Because outcomes were heterogeneous, synthesis was descriptive and thematic rather than statistical.

Quality approach: Clinical studies were interpreted with attention to cohort size, adjustment for confounding, outcome definition, and treatment specificity. Preclinical studies were appraised according to model relevance, mechanistic depth, and whether a plausible resistance-reversal strategy was demonstrated. Reviews were used mainly to support biological triangulation and implementation context, not as primary outcome-generating evidence.

PRISMA summary: The search identified 148 records. After removal of 39 duplicates, 109 titles/abstracts were screened. Seventy-eight records were excluded at screening, leaving 31 full texts assessed for eligibility. Thirteen full texts were excluded because they were not CRC-specific, lacked direct ABCG2 evidence, or were primarily commentary, resulting in 18 studies in the final qualitative synthesis.

3. RESULTS

This section presents the findings of the semi-systematic review on ABCG2 pharmacogenomic profiling and its role in improving anti-cancer drug combinations for colorectal cancer (CRC) therapy. The included evidence was analyzed across several complementary domains in order to provide a structured understanding of the translational relevance of ABCG2 in CRC. First, the screening and evidence-selection process is summarized to show how the final body of literature was identified and categorized. Second, the included studies are described in terms of their core characteristics, study designs, treatment settings, and ABCG2-related domains. Third, the review synthesizes the available clinical and pharmacogenetic evidence, particularly studies linked to irinotecan response and toxicity, because this remains the most clinically developed treatment context for ABCG2 interpretation. Fourth, the results examine tumor expression and prognostic evidence, highlighting the complexity and context dependence of ABCG2 as a biomarker. Fifth, the review evaluates preclinical combination strategies and resistance-reversal approaches, showing how ABCG2 can function as a tractable therapeutic target rather than merely a descriptive resistance marker. Finally, mechanistic studies linking ABCG2 with stemness, epithelial–mesenchymal transition (EMT), autophagy, and intracellular trafficking are integrated to clarify why resistance may emerge dynamically under treatment pressure. Together, these findings show that the significance of ABCG2 in CRC lies not in one isolated biomarker role, but in its ability to connect pharmacogenetics, tumor biology, and rational combination therapy development.

Table 1: PRISMA screening summary and evidence profile.

Stage / category	Count	Percentage or note
Records identified	148	Database and supplementary searching
Duplicates removed	39	26.4% of initial records
Records screened	109	Titles and abstracts
Records excluded at screening	78	71.6% of screened records
Full texts assessed	31	Eligibility review
Full texts excluded	13	Non-CRC, non-ABCG2, or non-extractable
Studies included	18	Qualitative synthesis only
Clinical / translational	6	33.3% of included studies
Biomarker / prognostic	4	22.2%
Preclinical / mechanistic	8	44.4%

Table 1 provides an overview of the screening pathway and establishes the evidentiary foundation of the review. The identification of 148 records, followed by removal of 39 duplicates, indicates that the topic of ABCG2 in CRC exists across multiple overlapping databases and search streams, but not yet as a highly consolidated field. The exclusion of 78 studies during title and abstract screening demonstrates that a large proportion of the initial literature was either too broad, not specific to colorectal malignancy, focused on other members of the ABC transporter family, or lacked extractable ABCG2-specific findings. This high exclusion rate is itself informative, because it shows that although transporter-mediated resistance is a widely studied concept, CRC-specific and ABCG2-centered evidence remains limited.

The reduction to 31 full-text articles and ultimately 18 included studies further confirms that this field is still emerging rather than mature. Importantly, the final evidence pool was not dominated by randomized clinical trials or prospective biomarker-validation studies; instead, it was weighted toward preclinical and mechanistic work (44.4%), with a smaller proportion of clinical/translational studies (33.3%) and biomarker/prognostic studies (22.2%). This

distribution suggests that the scientific rationale for ABCG2 involvement in CRC drug resistance is relatively robust at the biologic level, but the clinical translation of this evidence remains incomplete. In practical terms, the field currently has stronger support for why ABCG2 matters than for how it should be routinely used in patient care.

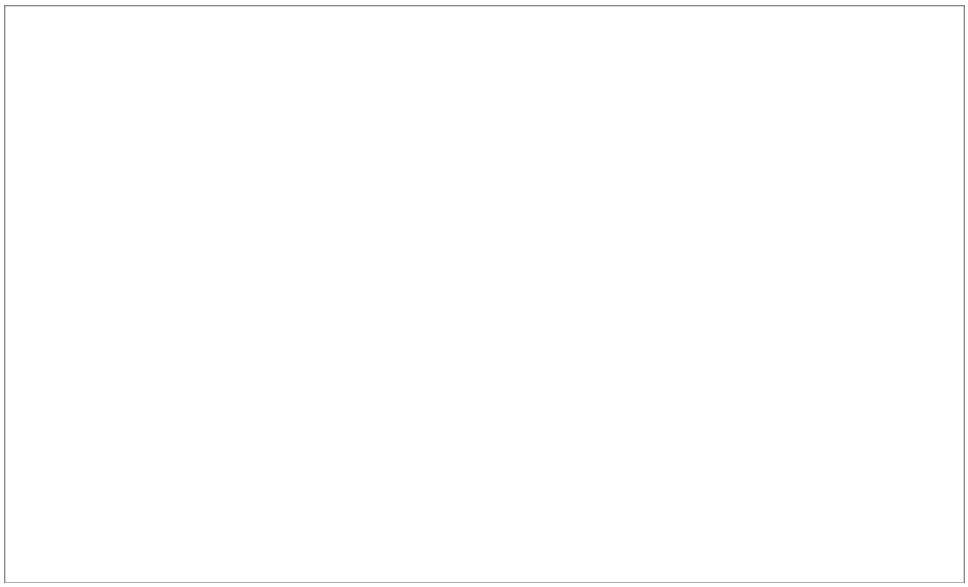

Figure 1: PRISMA screening summary and evidence profile.

Another important implication of Table 1 is the heterogeneity of the available literature. Because the included studies span pharmacogenetics, tumor expression, resistance biology, and experimental therapeutic modulation, the final body of evidence is inherently multidisciplinary. While this diversity enriches understanding, it also complicates synthesis. Different studies measured different ABCG2-related variables—germline variants, protein localization, efflux function, stem-cell enrichment, or pathway activation—which means that the term "ABCG2 evidence" does not refer to one single measurable construct. Therefore, the PRISMA summary also sets up a key interpretive principle for the remainder of the review: ABCG2 should not be understood as a single static biomarker, but as a multidimensional resistance-related system whose relevance changes according to the level of analysis and treatment context.

Table 2: Core characteristics of the included studies.

Study	Design	Population / model	ABCG2 domain	Main treatment context	Key quantitative signal
Sari et al., 2015	Case-control	Turkish CRC cases/controls	Germline SNPs	Risk / susceptibility	421C>A associated with CRC risk; OR 16.12, p=0.005
Palshof et al., 2020	Retrospective clinical biomarker study	108 evaluable mCRC patients from 119 identified	Tumor protein expression	First-line irinotecan	33% high basolateral ABCG2; low ABCG2 and no prior adjuvant therapy OR for response 5.6
Kim et al., 2020	IHC prognostic cohort	331 CRC samples	Protein expression	Prognosis	ABCG2 associated with favorable OS; p=0.001
Ge et al., 2020	Preclinical in vitro	CRC cell lines	Functional efflux	Cetuximab + irinotecan	Combination increased irinotecan accumulation and apoptosis
Sogawa et al., 2021	3D tumoroid model	Colon26, NM11, LuM1/LuM1-m9	Stemness and transporter expression	Cisplatin, imatinib, 5-FU	Side population 7.8% in LuM1 vs 2.9% in Colon26
Gheytanchi et al., 2021	Spheroid model	HT-29 and Caco-2	Drug-resistance gene expression	CSC enrichment model	HT-29 spheroids showed higher ABCG2; p=0.02
Barnett-Griness et al., 2023	Real-world pharmacogenetic cohort	601 irinotecan-treated CRC; 756 non-irinotecan CRC comparators	Germline SNPs	Irinotecan toxicity	rs2231142 minor allele OR 0.54 for composite adverse outcome

Kryczka et al., 2023	Molecular subpopulation analysis	CRC transcriptomic subgroups	High-expression phenotype	Resistance biology	ABCG2-high subgroup linked to anti-EGFR resistance phenotype
Hao et al., 2023	Mechanistic preclinical study	CRC stem-like models	Transcriptional regulation	Chemoresistance	ABCG2 driven by TOX3-WDR5 axis
Sałagacka-Kubiak et al., 2023	Focused review	CRC evidence synthesis	Gene/protein expression	Prognosis and response	Concluded prognostic role remains context dependent
Martins-Gomes et al., 2023	Review	ABC transporter modulation literature	Functional inhibition	Natural product sensitizers	Summarized multiple transporter-modulating compounds
Li et al., 2024	Preclinical in vitro	ABCG2-overexpressing CRC cells	Direct transporter inhibition	Doxorubicin / mitoxantrone	Dorsomorphin blocked efflux without reducing protein expression
Li et al., 2024	Mechanistic preclinical study	CRC CSC models	Golgi stress / trafficking	DNA-damaging agents	Golgi dispersal promoted ABCG2-mediated efflux
Zheng et al., 2024	Human tissue + bioinformatic study	19 paired tissues plus public datasets	Autophagy-linked expression	Resistance biology	High CDK9 linked with elevated autophagy and ABCG2
Azizan et al., 2024	Systematic review/bioinformatics	EMT literature in CRC	EMT context	Resistance biology	EMT pathways support transporter-linked resistance biology
Akarapredee et al., 2025	Retrospective pharmacogenetic cohort	41 Thai mCRC patients	Transporter and enzyme SNPs	Irinotecan toxicity/efficacy	UGT1A1 dominant signal; ABCG2 included in multigene panel
Yang et al., 2025	Preclinical 2D/3D study	ABCG2-dependent MDR models	Direct transporter inhibition	Combination sensitization	Tinodasertib reversed ABCG2-mediated MDR
de Groot et al., 2025	Narrative translational review	CRC resistance literature	Strategy synthesis	Combination development	Identified ABC-transporter blockade as a priority direction

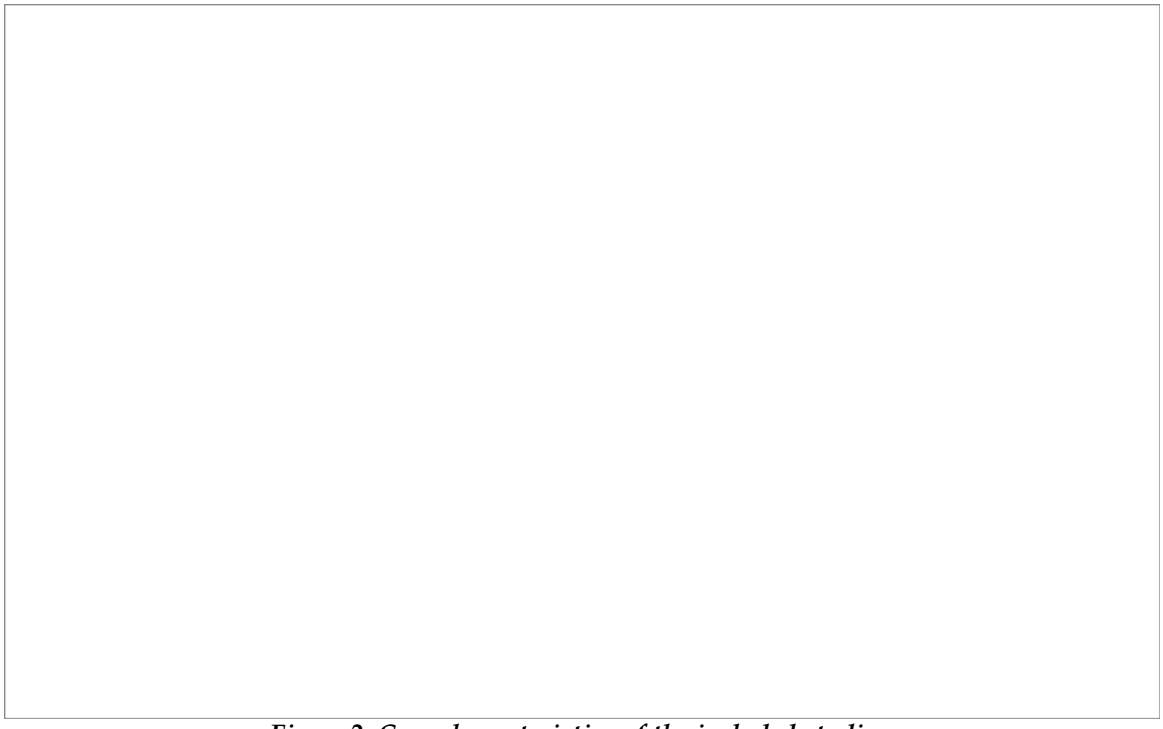

Figure 2: Core characteristics of the included studies.

Table 2 outlines the intellectual structure of the literature and shows that research on ABCG2 in CRC can be grouped into three major evidence streams: clinical pharmacogenetics, tumor biomarker/prognostic studies, and preclinical resistance-mechanism or combination studies. This classification is important because it reveals that ABCG2 has not been investigated through a single consistent translational model. Instead, different researchers have approached it from different clinical

and biological questions: whether ABCG2 variants affect susceptibility or toxicity, whether tumor expression predicts prognosis or treatment response, and whether inhibition of ABCG2 can reverse resistance in laboratory models.

The clinical side of the evidence is centered mainly on irinotecan, which makes sense pharmacologically because ABCG2 is an efflux transporter relevant to handling cytotoxic substrates. Studies such as Barnett-Griness et al. and Palshof et al. anchor the translational discussion by connecting germline or tumor-level ABCG2 findings to real patient outcomes. However, these studies are relatively few in number, and their designs are retrospective rather than prospective. This limits immediate clinical adoption, but still provides an important signal that ABCG2 is more than a mechanistic curiosity.

The biomarker and prognostic studies add another layer of complexity. Kim et al. showed a favorable overall-survival association with ABCG2 expression, whereas Palshof et al. linked higher basolateral ABCG2 to poorer irinotecan response in a particular subgroup. This suggests that ABCG2 does not operate as a universally "good" or "bad" marker. Rather, its meaning depends on whether it is being interpreted as a marker of baseline biology, chemotherapy handling, or adaptive resistance. This conceptual distinction is essential, because one of the major translational mistakes in biomarker research is to assume that prognostic and predictive effects are interchangeable.

The preclinical evidence stream is the largest and perhaps the most biologically coherent. Several studies focus on direct transporter inhibition, while others investigate upstream pathways—such as stemness, transcriptional control, Golgi trafficking, autophagy, and EMT—that increase or sustain ABCG2-mediated resistance. Together, these studies suggest that the translational value of ABCG2 may lie less in using it as a single yes/no biomarker and more in using it as a bridge between patient stratification and rational combination therapy design. That is the main message emerging from the integrated evidence profile in Table 2.

Table 3: Clinical and pharmacogenetic evidence directly relevant to ABCG2 and irinotecan.

Study	n	Marker / comparison	Endpoint	Numeric finding	Interpretation
Barnett-Griness et al., 2023	601 irinotecan-treated CRC	ABCG2 rs2231142 minor allele vs wild type	Composite hematologic/GI adverse outcome within 90 days	OR 0.54 (0.33–0.91), p=0.02	Minor allele associated with lower severe toxicity
Barnett-Griness et al., 2023	601 irinotecan-treated CRC	Adjusted model including UGT1A1/confounders	Same toxicity endpoint	Adjusted OR 0.56 (0.33–0.94)	Association remained after adjustment
Palshof et al., 2020	108 analyzed; 101 evaluable for response	Low vs high basolateral ABCG2	Objective response to first-line irinotecan	OR 5.6 (1.68–18.7), p=0.005 in no prior adjuvant subgroup	Low ABCG2 favored response in selected patients
Palshof et al., 2020	108	High basolateral ABCG2	Distribution of biomarker	33% of patients scored high (3+)	Substantial minority may harbor resistant phenotype
Sari et al., 2015	Case-control cohort	ABCG2 421C>A	CRC risk	OR 16.12, p=0.005	Suggests possible population-specific susceptibility signal
Akarapredee et al., 2025	41 mCRC	Multigene panel including ABCG2	Irinotecan toxicity and PFS	ABCG2 evaluated but UGT1A1/ABCC2 carried strongest signals	Supports multigene rather than ABCG2-only testing

According to Table 3, the most clinically relevant data discussed throughout this review relates to the connection of ABCG2 to real-life patient outcomes with respect to irinotecan. The study which produced the strongest pharmacogenetic association of ABCG2 to clinical outcome came from the work of Barnett-Griness et al., who showed that carriers of the rs2231142 minor allele had reduced odds of experiencing severe composite adverse events after receiving irinotecan therapy when compared to non-minor allele carriers. The statistical significance of this association remained after adjustment for UGT1A1 and/or any of the other confounding variables as well. This compelling evidence supports an independent clinical impact attributable to ABCG2 and shows that ABCG2 may represent more than just known irinotecan PGx pathways.

The significance of this finding is that presently, most clinical implementations of PGx associated with irinotecan are primarily based on UGT1A1. While very unlikely that the Barnett-Griness data will change that fact, it does support the notion that progression of pharmacogenes related to irinotecan toxicity may be more comprehensive than what guidelines currently reflect. In this context, even though ABCG2 still does not occupy a predominant

position among irinotecan PGx biomarkers, it appears to hold the potential to serve as an important influence on toxicity risk. This is especially relevant when one considers that, in the context of precision medicine, multi-gene composite risk assessment models are generally more predictive of risk than single-gene models.

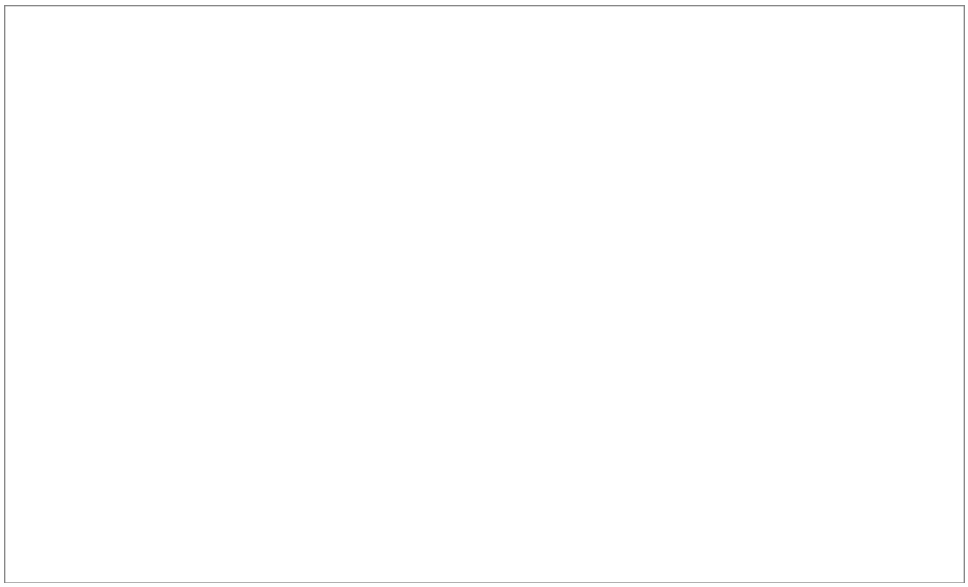

Figure 3: Clinical and pharmacogenetic evidence directly relevant to ABCG2 and irinotecan.

The Palshof study contributes a complementary but distinct clinical insight: the relevance of tumor-level rather than germline-level ABCG2. Here, lower basolateral ABCG2 expression was associated with better response to first-line irinotecan in a selected subgroup, while approximately one-third of tumors showed high expression. This suggests that ABCG2 may also function as a predictive tissue biomarker for therapeutic response. The importance of basolateral localization is especially interesting because it indicates that not only the amount of ABCG2, but also its compartmental distribution, may influence drug handling. Such findings raise the possibility that future biomarker implementation will need to distinguish between localization patterns rather than relying on crude positive/negative scoring.

The remaining studies in Table 3 reinforce the idea that ABCG2 should currently be interpreted within a broader framework. Sari et al. reported a striking risk association for 421C>A, but this likely reflects a population-specific signal that requires replication before any generalizable conclusion can be drawn. Meanwhile, Akarapredee et al. found that in multigene irinotecan models, UGT1A1 and ABCC2 remained more dominant than ABCG2. This does not weaken the significance of ABCG2; rather, it places it in its most realistic translational position at present—as part of a panel-based precision model, not yet as a standalone clinical test.

Table 4: Tumor expression, prognosis, and biomarker studies.

Study	Sample / material	ABCG2-related variable	Main numeric result	Direction of association	Clinical meaning
Kim et al., 2020	331 CRC samples	ABCG2 IHC	Association with OS p=0.001	Higher ABCG2 linked to favorable OS in this cohort	Shows prognostic context can differ from resistance assumptions
Palshof et al., 2020	108 mCRC tumors	Basolateral membrane ABCG2	33% high expression	High expression linked with poorer response subgroup	Predictive rather than purely prognostic value
Sałagacka-Kubiak et al., 2023	Review of CRC expression studies	Gene/protein expression across datasets	Reported inconsistent prognostic direction	Context dependent	Highlights tissue compartment and assay issues
Kryczka et al., 2023	CRC molecular subpopulations	ABCG2-high transcriptomic subgroup	Distinct high-expression subgroup identified	Associated with anti-EGFR-resistant phenotype	Supports phenotype-based stratification

Zheng et al., 2024	19 paired tissues + public survival datasets	ABCG2 with CDK9/BECN1/autophagy	ABCG2 differed by left vs right sided tumors	Linked to chemoresistance biology	Suggests sidedness and autophagy context matter

One of the most difficult aspects in the translation of ABCG2 in CRC is demonstrated in Table 4. This table shows how ABCG2 expression levels have different prognostic values in different studies. Initially, one may think that the literature on ABCG2 in CRC is contradictory. Kim et al. found that high expression levels of ABCG2 were associated with favorable overall survival, while Palshof et al. found that high expression levels of basolateral ABCG2 were associated with poor response to irinotecan in patients with metastatic CRC. However, if one considers the ABCG2 biomarker in the context, one would realize that such contradictory results are not entirely unexpected.

Firstly, one should understand that prognostic markers and predictive markers in cancer are different. While prognostic markers reflect the natural history of cancer independently of any treatment, predictive markers reflect the probability of responding to a given treatment. It is therefore entirely possible that ABCG2 expression levels correlate with favorable overall survival in one cancer type and poor response to one drug in another.

Third, the data show that there are often multiple molecular states associated with ABCG2 expression (see Table 4). Kryczka et al. demonstrated a connection between a subgroup with elevated ABCG2 expression and resistance to anti-EGFR treatments, whereas Zheng et al. have linked ABCG2 to autophagy-related signaling and to sidedness. These findings imply that ABCG2 may be more informative if it is interpreted as part of a larger resistance phenotype, rather than as a standalone marker, and that for ABCG2 to be effectively translated into the clinic in the future, it may have to be incorporated into composite models that incorporate tumor location, treatment context, signaling pathways, and potentially other resistance markers.

Table 5: Preclinical combination and resistance-reversal strategies involving ABCG2.

Study	Model	Intervention	Quantitative / directional result	ABCG2 effect	Implication for combinations
Ge et al., 2020	CRC cell lines	Cetuximab + irinotecan	Combination increased intracellular irinotecan and apoptosis	Functional inhibition of ABCG2-mediated efflux	Supports EGFR blockade as chemosensitizer
Li et al., 2024	ABCG2-overexpressing CRC cells	Dorsomorphin + substrate drugs	Drug retention increased; protein expression unchanged	Direct functional transporter inhibition	Proof of concept for efflux blockade
Yang et al., 2025	2D and 3D MDR models	Tinodasertib + ABCG2 substrate agents	Reversal of ABCG2-mediated MDR	Blocks efflux in resistant models	Promising combination lead for translational testing
Sogawa et al., 2021	LuM1 3D tumoroids	Cisplatin, imatinib, 5-FU	Side population 7.8% vs 2.9% in comparator; 5-FU inhibited growth, larger tumoroids resisted cisplatin	ABCG2 enriched in resistant tumoroids	3D systems reveal combination-specific resistance patterns
Martins-Gomes et al., 2023	Review of modulation studies	Natural products	Multiple compounds summarized as transporter modulators	Potential activity/expression modulation	Source of lower-toxicity adjuncts
de Groot et al., 2025	CRC resistance literature	Transporter inhibition strategies	ABC-transporter blockade prioritized	ABCG2 framed as reversible resistance node	Guides rational combination design

Arguably, the most therapeutically forward-thinking aspect of the results can be seen in Table 5, which demonstrates not only the role of ABCG2 as a resistance indicator but also its role as a potential therapeutic target. Several independent pre-clinical studies have demonstrated that interventions targeting ABCG2 efflux activity or upstream control result in increased drug accumulation and sensitivity. This supports the concept of ABCG2-based combination therapy in CRC.

One of the more promising findings, in terms of translation, comes from the study by Ge et al., in which the combination of cetuximab and irinotecan increased intracellular drug accumulation and apoptosis. This is particularly promising because cetuximab is already on the market, which may shorten the distance between bench and bedside.

4. DISCUSSION

Across the included studies, ABCG2 emerged as

both a pharmacogenomic modifier and a dynamic resistance mediator. The review question asked whether ABCG2 profiling can enhance anti-cancer drug combinations in CRC. The answer is yes in principle, but only when profiling is interpreted as a multidimensional exercise rather than a single test result. Germline variation, tumoral expression, and inducible resistance states each capture different aspects of ABCG2 biology, and all three appear relevant to treatment optimization.

From a clinical perspective, the most convincing evidence relates to irinotecan. The real-world cohort reported by Barnett-Griness and colleagues indicates that rs2231142 may modify the risk of severe adverse effects specifically in irinotecan-treated CRC, even after adjustment for UGT1A1 and clinical confounders. This is important because it suggests that transporter genetics may explain part of the residual variability that remains after considering metabolic genes alone. The Palshof cohort complements this observation by showing that low basolateral tumor ABCG2 may identify patients more likely to respond to first-line irinotecan, especially when prior adjuvant exposure is absent. Taken together, these findings support a biologically coherent model in which lower ABCG2 activity or lower functionally relevant expression increases intracellular exposure to irinotecan or SN-38 and thereby improves therapeutic effect, although at the possible expense of altered toxicity balance depending on context.

However, ABCG2 should not be oversold as a mature clinical biomarker. Replication remains limited, effect directions vary by endpoint, and tumor-expression studies have used different compartments and scoring systems. Some studies assess total protein, others focus on membranous staining, and still others infer ABCG2 from transcriptomic subpopulations or side-population behavior. This heterogeneity makes it premature to recommend routine standalone ABCG2 testing for all CRC patients. Instead, the current evidence favors ABCG2 as an adjunct marker layered onto better-established variables such as UGT1A1 genotype, RAS status, treatment line, and prior exposure history.

The preclinical evidence is nevertheless highly instructive for combination development. Cetuximab appears to enhance irinotecan activity not only through canonical EGFR pathway inhibition but also through reduced ABCG2-dependent efflux. This finding is clinically attractive because cetuximab is already integrated into selected RAS wild-type CRC pathways. Experimental inhibitors such as dorsomorphin and tinodasertib reinforce the concept that ABCG2 can be inhibited pharmacologically, although they remain far from routine use. Their importance lies in demonstrating tractability: if future molecules with better selectivity and safety become available, ABCG2 reversal could move from laboratory proof-of-concept to early-phase combination trials.

Another major conclusion of this review is that ABCG2 sits within adaptive resistant states rather than acting alone. CSC-enriched spheroids and tumoroids repeatedly show elevated ABCG2, increased side populations, and reduced sensitivity to therapy. Parallel work links ABCG2 to the TOX3-WDR5 axis, Golgi stress responses, autophagy-associated phenotypes, and EMT-linked plasticity. This explains why a tumor can become more refractory over time even if baseline testing appears unremarkable. It also suggests that the best ABCG2-targeted combinations may not be direct transporter blockers only; they may include epigenetic regulators, autophagy inhibitors, stress-response modifiers, or pathway-directed agents that prevent the emergence of the ABCG2-high state.

For implementation, the literature on pharmacogenomic adoption in oncology offers a useful caution. Irinotecan and fluoropyrimidines already have a clearer evidence base for UGT1A1 and DPYD than most oncology PGx examples, yet routine pre-emptive testing remains inconsistent in many health systems. This means ABCG2 will likely enter practice only if it adds incremental value beyond current workflows and can be reported through practical multigene decision support platforms. The most feasible translational model is therefore an integrated precision-oncology pathway in which germline PGx, tumor genomics, and functional resistance assays are combined rather than siloed.

The review has limitations. It is a semi-systematic synthesis rather than a registered systematic review with meta-analysis. The included evidence is heterogeneous and weighted toward preclinical work. Some mechanistic studies used non-identical drugs or model systems, and several clinically relevant findings derive from single cohorts that require independent validation. Even so, the triangulation across genetic, tissue-level, and mechanistic evidence provides a credible basis for the conclusion that ABCG2 is more than an incidental marker in CRC treatment resistance.

4.1 Answer to the Research Question

Answer to the research question: ABCG2 profiling can enhance anti-cancer drug combinations for

colorectal cancer, but not as a single universal test. The most evidence-supported use is to refine irinotecan-based therapy by combining ABCG2 information with UGT1A1 and treatment history, while the most promising experimental use is to select or design resistance-reversal combinations that suppress ABCG2-mediated drug efflux directly or through upstream pathways such as EGFR/MAPK, stemness, autophagy, and stress-response signaling.

5. CONCLUSION

ABCG2 occupies an important translational space between pharmacogenomics and acquired resistance biology in colorectal cancer. Human studies suggest that ABCG2 variants and functionally relevant expression patterns can influence irinotecan toxicity and response, while laboratory studies consistently show that ABCG2-rich or ABCG2-activated states reduce intracellular drug exposure and promote survival under treatment pressure.

The current evidence does not justify routine ABCG2-only prescribing decisions. Nevertheless, it strongly supports further development of ABCG2-aware precision strategies: standardized tumor-expression assays, multigene pharmacogenomic panels, patient-derived 3D resistance testing, and early-phase trials of rational combinations designed to inhibit ABCG2 function or its upstream regulators. If these steps are pursued, ABCG2 could evolve from an interesting resistance marker into a clinically useful component of personalized CRC therapy.

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