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Pharmacogenomics in solid tumors: Integrating germline and somatic genetic variability for precision oncology

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Abstract

Background: Solid tumors exhibit substantial interindividual variability in therapeutic response and drug-related toxicity, which cannot be fully explained by clinical or tumor-specific factors alone. Pharmacogenomics has emerged as a critical component of precision oncology by elucidating how both germline and somatic genetic variability influence anticancer drug efficacy and safety.

Objective: This review provides a comprehensive and clinically oriented overview of pharmacogenomics in solid tumour's, highlighting actionable gene–drug associations, translational relevance, implementation challenges, and emerging innovations shaping future oncology practice.

Methods: A narrative review of peer-reviewed literature published between 2020 and 2026 was conducted using PubMed, EMBASE, Web of Science, and Google Scholar. Human studies, systematic reviews, meta-analyses, and clinical guidelines focusing on pharmacogenomic biomarkers and gene–drug interactions in solid tumors were included.

Results: Germline variants in key drug-metabolizing enzymes, including *CYP2D6, DPYD, and UGT1A1,* significantly influence drug exposure, toxicity risk, and treatment outcomes across multiple solid tumors. Somatic alterations such as *EGFR, KRAS,* and *BRCA1/2* mutations guide targeted therapy selection, resistance prediction, and tumor-agnostic treatment strategies. Despite robust evidence supporting pharmacogenomic-guided therapy, clinical implementation remains inconsistent due to infrastructural limitations, cost concerns, and gaps in clinician education.

Conclusion: Pharmacogenomics represents a foundational pillar of precision oncology by integrating host and tumor genetic information to optimize therapeutic decision-making. Advances in polygenic modeling, liquid biopsy technologies, artificial intelligence, and multi-omics integration are expected to accelerate clinical adoption. Systematic implementation of pharmacogenomics has the potential to improve treatment efficacy, reduce toxicity, and enhance patient outcomes in solid tumors.

Keywords: Pharmacogenomics; Solid tumors; Precision oncology; Genetic variability; Gene–drug interactions

1. Introduction

Solid tumors represent a biologically diverse group of malignancies characterized by marked heterogeneity in disease progression, therapeutic response, and clinical outcomes. Despite major advances in oncology, including the development of targeted therapies and immunotherapeutic agents, a substantial proportion of patients continue to experience suboptimal treatment efficacy or severe drug-related toxicity. This variability cannot be fully explained by

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clinical parameters alone and has drawn increasing attention to the role of genetic factors in modulating drug response. [1] [2]

Pharmacogenomics, the study of how genetic variation influences drug pharmacokinetics and pharmacodynamics, has emerged as a critical component of precision oncology. Traditionally, cancer treatment personalization has focused predominantly on tumor-specific somatic alterations that guide the selection of targeted therapies. While this approach has transformed the management of several solid tumors, it overlooks the contribution of germline genetic variability, which governs drug absorption, metabolism, transport, and elimination. So patients with identical tumor genotypes may respond very differently to the same therapy. [3]

In solid tumors, pharmacogenomic variability influences treatment outcomes across the therapeutic spectrum, including cytotoxic chemotherapy, hormonal therapy, targeted agents, and, increasingly, immunotherapies. Germline variants in drug-metabolizing enzymes and transporters can predispose patients to life-threatening toxicities or therapeutic failure, whereas somatic mutations within tumors dictate sensitivity or resistance to specific agents. Integrating both dimensions is therefore essential for truly individualized cancer care. [3] [4]

Over the past decade, technological advancements in genomic sequencing, bioinformatics, and clinical decision support have accelerated the translation of pharmacogenomics from research settings into clinical practice. However, despite growing evidence and guideline recommendations, widespread clinical adoption remains inconsistent. [3] [4]

1.1. Clinical Decision-Making Perspective

Pharmacogenomic-guided prescribing represents a shift from reactive management of toxicity to proactive risk stratification, allowing clinicians to anticipate adverse drug reactions and optimize therapy before treatment initiation.

This review aims to provide a comprehensive and clinically oriented overview of pharmacogenomics in solid tumors, emphasizing recent advances, translational relevance, and future directions that may facilitate routine implementation in oncology practice.

2. Methods

This review was designed as a comprehensive narrative synthesis of contemporary evidence addressing the role of pharmacogenomics in solid tumor management. A structured literature search was conducted across major biomedical databases, including PubMed, EMBASE, Web of Science, and Google Scholar. The search strategy employed combinations of keywords related to pharmacogenomics, solid tumors, genetic variability, drug response, and precision oncology.

To ensure clinical relevance and contemporary applicability, only peer-reviewed human studies published between 2020 and 2026 were considered. Eligible publications included original research articles, systematic reviews, meta-analyses, and clinical guidelines focusing on gene–drug interactions, pharmacogenomic biomarkers, and translational oncology. Preclinical studies, editorials lacking original data, and publications outside the defined time frame were excluded.

Data extraction focused on identifying clinically actionable pharmacogenomic markers, their associated anticancer agents, tumor types, and reported clinical outcomes, including efficacy, toxicity, and resistance. Findings were synthesized qualitatively, with emphasis on biological plausibility, strength of clinical evidence, and potential for real-world implementation. This approach was chosen to provide a balanced and integrative perspective rather than a purely quantitative comparison.

2.1. Germline pharmacogenomics in solid tumors

2.1.1. CYP2D6 and Endocrine Therapy in Breast Cancer

Tamoxifen remains a cornerstone of therapy for estrogen receptor-positive breast cancer. Its clinical efficacy depends on hepatic conversion to endoxifen, a process mediated primarily by CYP2D6. Genetic polymorphisms leading to poor or intermediate metabolizer phenotypes result in reduced endoxifen exposure and inferior clinical outcomes.

Recent studies demonstrate that CYP2D6 genotype-guided therapy can improve disease-free survival by enabling alternative endocrine strategies or dose optimization. While controversy existed in earlier literature, post-2020 meta-analyses have reinforced the clinical relevance of CYP2D6 testing, particularly in premenopausal patients. [5]

2.1.2. DPYD Variants and Fluoro pyrimidine Toxicity

Fluoropyrimidines such as 5-fluorouracil and capecitabine are widely used in colorectal, gastric, and breast cancers. Dihydropyrimidine dehydrogenase (DPD), encoded by *DPYD*, is responsible for catabolizing over 80% of administered 5-FU.

Patients with partial or complete DPD deficiency face a dramatically increased risk of life-threatening toxicity, including myelosuppression, mucositis, neurotoxicity, and death. Prospective DPYD genotyping has been shown to significantly reduce severe toxicity and healthcare costs, leading several regulatory agencies to recommend pre-treatment testing. [6]

2.1.3. UGT1A1 Polymorphisms and Irinotecan

Irinotecan is metabolized to SN-38, which is detoxified through glucuronidation by UGT1A1.[7] The UGT1A1*28 allele reduces enzymatic activity, leading to accumulation of SN-38 and increased risk of neutropenia and diarrhea.[8]

Clinical studies support dose reduction in homozygous *28/*28 carriers, demonstrating improved safety without compromising antitumor efficacy. This represents one of the most robust examples of pharmacogenomic-guided dosing in oncology. [7] [8]

2.2. Somatic pharmacogenomics and targeted therapy

2.2.1. EGFR Mutations in Lung Cancer

Activating EGFR mutations define a molecular subset of non-small cell lung cancer with dramatic sensitivity to EGFR tyrosine kinase inhibitors.[9] Resistance mutations, such as T790M, further highlight the dynamic nature of somatic pharmacogenomics and the need for longitudinal genomic monitoring. [3]

2.2.2. KRAS Mutations and Resistance Mechanisms

KRAS mutations confer intrinsic resistance to anti-EGFR monoclonal antibodies in colorectal cancer. [10] Beyond therapy exclusion, emerging KRAS inhibitors illustrate how pharmacogenomics can transform historically “undruggable” targets into actionable pathways. [4]

2.2.3. BRCA1/2 and Synthetic Lethality

BRCA-mutated tumors exhibit impaired DNA repair, rendering them highly sensitive to PARP inhibitors. This paradigm has expanded beyond breast and ovarian cancer to include prostate and pancreatic malignancies, underscoring the tumor-agnostic potential of pharmacogenomics. [11] [12]

3. Clinical implementation challenges

Despite compelling evidence, routine pharmacogenomic testing faces barriers:

- Limited access to testing infrastructure
- Cost and reimbursement issues
- Lack of clinician education
- Clinician discomfort with genetics
- Need for structured education
- Underrepresentation of diverse populations in genomic datasets [13] [2]

These challenges highlight the need for standardized testing frameworks and interdisciplinary collaboration between oncologists, pharmacists, and geneticists.

4. Pharmacogenomics across different therapeutic classes

4.1. Cytotoxic Chemotherapy

Cytotoxic agents remain a cornerstone of solid tumor treatment. Pharmacogenomic variability in enzymes involved in drug metabolism and detoxification significantly influences toxicity profiles and dose tolerance. Incorporating pharmacogenomic data into chemotherapy planning enables safer administration of agents with narrow therapeutic indices.

4.2. Endocrine Therapy

Hormonal therapies, particularly in breast and prostate cancers, are administered over prolonged durations. Genetic variability affecting drug activation and metabolism can lead to underexposure or therapeutic failure, highlighting the importance of pharmacogenomic consideration in long-term cancer management.

4.3. Targeted Therapy

Targeted agents exemplify the success of molecular oncology; however, host genetic factors continue to influence drug exposure and adverse events. Pharmacogenomics complements tumor mutation profiling by addressing variability in drug handling and off-target effects.

4.4. Immunotherapy

Although immunotherapies are not traditionally dose-adjusted, emerging evidence suggests that host genetics may influence immune-related adverse events and response durability. Pharmacogenomic research in this area is still evolving but represents an important future frontier. [1] [3] [8]

5. Implementation models in clinical practice

Successful pharmacogenomic implementation requires multidisciplinary collaboration involving oncologists, clinical pharmacists, geneticists, and bioinformaticians. Embedding pharmacogenomic data into electronic health records with clinical decision support tools can streamline interpretation and reduce clinician burden.

Clinical pharmacists play a pivotal role in the interpretation of pharmacogenomic results, dose optimization, and patient counseling, thereby acting as a bridge between genetic data and oncological decision-making.

Preemptive pharmacogenomic testing models, where genetic information is generated before treatment decisions are made, may offer particular advantages in oncology, where treatment timelines are often compressed. Such models allow rapid, informed decision-making without delaying therapy initiation.

Education and training of healthcare professionals remain critical. Incorporating pharmacogenomics into medical and pharmacy curricula will ensure that future clinicians are equipped to interpret and apply genetic data responsibly.

A major limitation in current pharmacogenomic evidence is the underrepresentation of diverse populations, which may limit the generalizability of existing recommendations. Addressing population-specific genetic variability is essential to ensure equitable implementation of precision oncology worldwide.

6. Future directions

6.1. Polygenic and Pathway-Based Models

The future of pharmacogenomics in solid tumors lies in expanding its scope beyond single-gene testing toward more comprehensive, systems-based approaches. While current clinical implementation often relies on individual gene–drug pairs, drug response is inherently multifactorial and influenced by complex genetic networks. Polygenic risk models that integrate multiple variants across pharmacokinetic and pharmacodynamic pathways may offer superior predictive accuracy and enable more refined treatment personalization. [14]

6.2. Liquid Biopsy Applications

Another promising direction is the integration of pharmacogenomics with liquid biopsy technologies. Circulating tumor DNA and other circulating biomarkers allow real-time assessment of tumor evolution, resistance mechanisms, and dynamic pharmacogenomic profiles. This approach has the potential to support adaptive treatment strategies, particularly in advanced solid tumors where clonal evolution under therapeutic pressure is common. [15]

6.3. Artificial Intelligence Integration

Artificial intelligence and machine learning are expected to play an increasingly central role in pharmacogenomics. By integrating genomic data with clinical variables, imaging, and electronic health records, AI-driven models may enable predictive analytics for drug response and toxicity. Such tools could assist clinicians in selecting optimal therapies and dosing regimens at the point of care. [16]

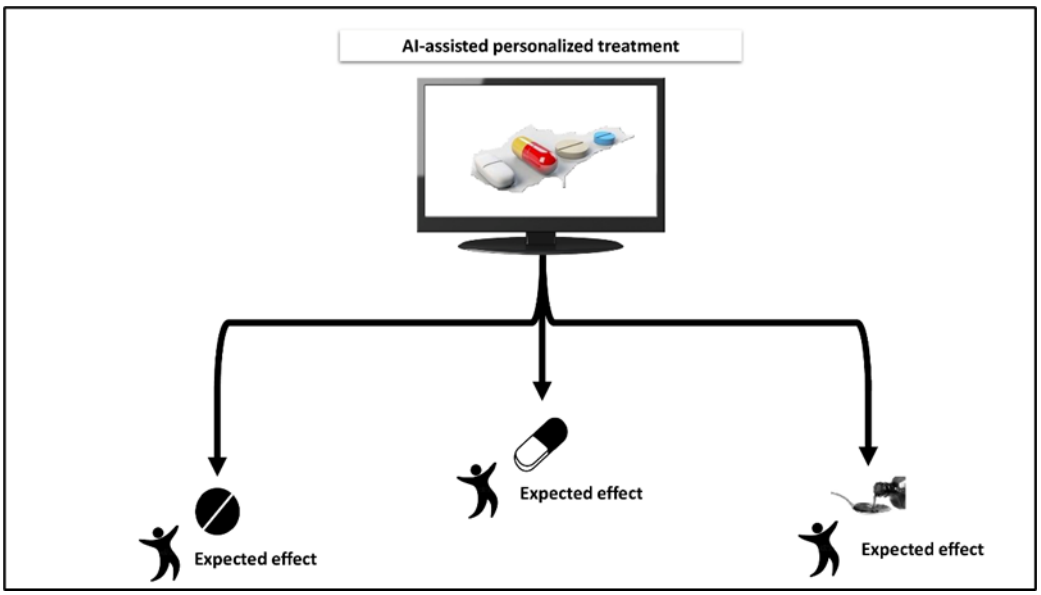

Figure 1 AI-assisted personalized treatment

6.4. Multi-Omics Precision Oncology

The integration of pharmacogenomics with other omics disciplines including transcriptomics, proteomics, metabolomics, and epigenomics represents a critical step toward holistic precision oncology. Multi-omics approaches can capture regulatory and functional layers of drug response that are not evident from genomic data alone, providing a more complete understanding of treatment variability.

To realize these advances, future efforts must also address implementation challenges. Standardization of testing protocols, expansion of genomic reference databases to include diverse populations, clinician education, and supportive regulatory frameworks will be essential to ensure equitable and effective adoption of pharmacogenomics worldwide. [16]

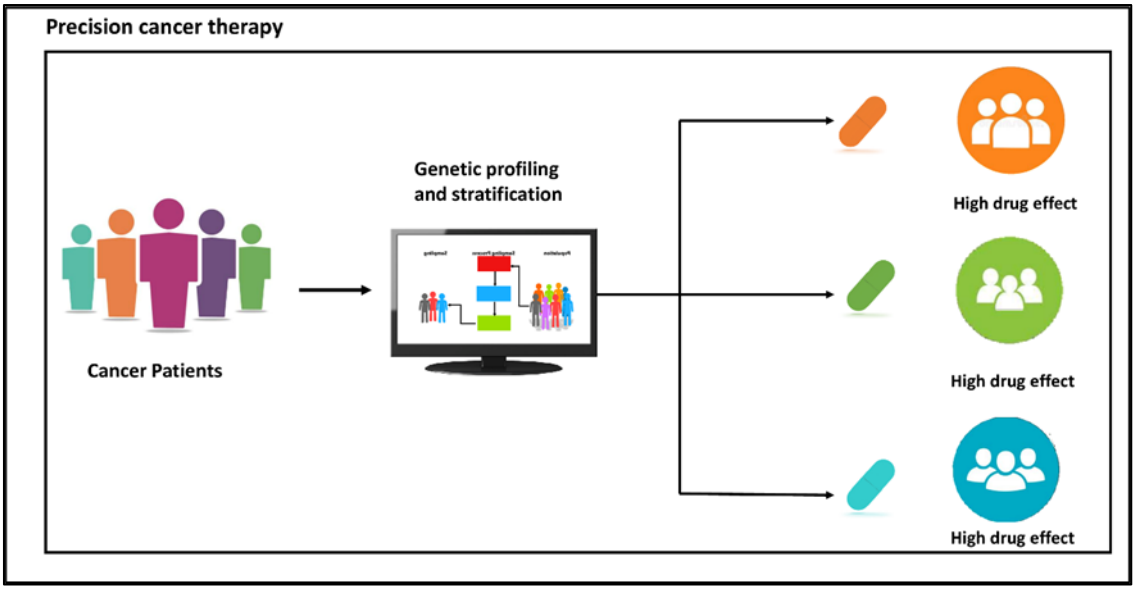

Figure 2 Precision cancer therapy

6.5. Tumor-Agnostic Pharmacogenomics

Future pharmacogenomic strategies may evolve toward tumor-agnostic, patient-centric models, where host genetic variability guides therapy selection independently of tumor origin.

6.6. Digital Health Integration

Integration of pharmacogenomic data into electronic health records with real-time clinical decision support systems may facilitate clinician adoption and reduce interpretative burden.

7. Conclusion

Pharmacogenomics has emerged as a foundational pillar of precision oncology, offering a mechanistic explanation for interindividual variability in drug response and toxicity among patients with solid tumors. By integrating germline and somatic genetic information into therapeutic decision-making, pharmacogenomic approaches enable more rational drug selection, individualized dosing, and improved patient safety. [1] [2]

Recent advances have demonstrated that pharmacogenomics is not limited to experimental settings but has tangible clinical utility across multiple tumor types and therapeutic classes. However, its full potential remains unrealized due to implementation barriers, limited infrastructure, and gaps in clinician awareness. Addressing these challenges will require coordinated efforts among researchers, clinicians, healthcare systems, and policymakers. [3]

Looking ahead, the convergence of pharmacogenomics with emerging technologies such as liquid biopsies, artificial intelligence, and multi-omics analytics is poised to redefine cancer treatment paradigms. As these innovations mature, pharmacogenomics is expected to transition from a supplementary tool to a routine component of oncology practice, ultimately improving therapeutic outcomes and quality of life for patients with solid tumors. [13]

Compliance with ethical standards

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