Specialty Journal of Pharmacognosy, Phytochemistry, and Biotechnology
ISSN: 3062-441X
2022, Volume 2, Page No: 167-177

Available online at: www.galaxypub.co/page/journals

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Interpreting Genomic Alterations to Understand Effectiveness and Adverse Reactions to Cancer Therapeutics: Insights from the Oncology Pharmacy Field

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Received: 02 August 2022; **Revised:** 27 October 2022; **Accepted:** 28 October 2022

ABSTRACT

This paper explores emerging areas of pharmacogenomics that are becoming increasingly relevant to contemporary oncology pharmacy practice. The literature examined for this review was primarily drawn from recently approved therapeutics issued by the U.S. Food and Drug Administration and from newly incorporated treatment protocols within the National Comprehensive Cancer Network. The discussion highlights major pharmacogenomic themes, such as genomic variations that shape drug biotransformation, influence therapeutic response, and modify molecular targets; it also integrates significant clinical developments to offer a comprehensive perspective. The expanding repertoire of pharmacogenomic tools provides a robust platform for practice evolution and signals a transformative movement toward highly individualized treatment strategies.

Keywords: Tumor-agnostic drug, cell-free DNA, Pharmacogenomics, Circulating tumor DNA, Precision medicine, Next-generation sequencing

How to Cite This Article: Rezaei M, Karimi A, Mohammadi R, Jalali S, Farhadi H. Interpreting Genomic Alterations to Understand Effectiveness and Adverse Reactions to Cancer Therapeutics: Insights from the Oncology Pharmacy Field. Spec J Pharmacogn Phytochem Biotechnol. 2022;2:167-77. https://doi.org/10.51847/fuflRMnfNT

Introduction

Pharmacogenomics—first introduced as a term in 1997—focuses on how medications behave in the context of individual genetic variations, including mutations, shifts in gene expression, and allele diversity. Over the past several decades, discoveries in this field have accelerated considerably. Current areas receiving significant attention include multidrug-resistance mechanisms, polymorphisms affecting drug biotransformation, and emerging directions in precision oncology.

This discipline has laid the groundwork for aligning therapeutic choices with each patient's genomic profile. In 2022, the American Society of Clinical Oncology released its Provisional Clinical Opinion on Somatic Genomic Testing for Patients with Metastatic or Advanced Cancer, outlining when next-generation sequencing is appropriate, distinguishing among assay types, and clarifying how results should be translated into treatment strategies. The document also consolidates essential terminology used across precision oncology [1], serving as an enduring reference point for clinical practice.

Mastery of molecular testing methods has become crucial for delivering individualized oncology care. Numerous gene-drug relationships now guide therapeutic planning. For instance, EGFR exon 19 deletions in non-small cell lung cancer generate highly responsive, sensitizing lesions that show notable benefit from tyrosine kinase inhibitors such as osimertinib, furmonertinib, and aumolertinib [2]. This represents a prototypical precision-oncology gene-drug pairing. Similarly, pharmacogenomically relevant drug metabolism examples—such as DPyD wild-type carriers who process 5-fluorouracil, capecitabine, and tegafur normally—remain important for clinical decision-making [3].

Given both the rapid evolution and complexity of the field, a comprehensive pharmacogenomics review is highly warranted. Continued advancements in sequencing have sharpened our ability to detect clinically actionable

alterations with remarkable specificity and speed. As a result, the incorporation of genomic data into routine care is driving a transformative shift toward more tailored and effective treatment paradigms.

This review aims to equip clinicians treating cancer with a scientifically grounded reference in pharmacogenomics. By integrating genomic insight into oncology workflows, practitioners can refine therapeutic selection and personalize dosing in accordance with each patient's genetic profile. Because genetic differences influence both therapeutic impact and adverse effects, harnessing these data enables improved survival outcomes while reducing treatment-related harm.

This work supports oncologists, pharmacists, and nurses in navigating the pharmacogenomic considerations embedded within clinical decision-making. It additionally outlines the genomic basis for select high-profile agents and clarifies how their mechanisms support formulary or reimbursement decisions within managed care settings.

Understanding cell-free DNA assays

Constructing a comprehensive pharmacogenetic/pharmacogenomic framework relies heavily on specialized molecular testing tools—such as sequencing, immunohistochemistry, flow cytometry, and single-cell platforms. While each method offers distinct benefits and limitations, one technology has risen to particular prominence: cell-free DNA (cfDNA) assays. These tests function as a "supercement-level" tool, enabling extraordinarily high-throughput genetic interrogation. With a single sample and a turnaround of 5–14 days, cfDNA assays can examine millions of genomic alterations simultaneously, dramatically accelerating the pace of pharmacogenomic evaluation and informing subsequent steps including interpretation, therapy selection, and clinical decision-making.

cfDNA testing—commonly described as liquid biopsy—provides a non-invasive approach to identifying DNA fragments circulating in the bloodstream. These fragments originate from many cell populations, including tumor cells, and can reveal somatic mutations, chromosomal abnormalities, and additional molecular signatures relevant to malignancy. In oncology, cfDNA becomes particularly valuable when disease progresses across several metastatic sites, as it captures newly emerging mutations that may not be detected in archival tissue. Though ctDNA and cfDNA are technically distinct terms, they are used interchangeably in many clinical settings.

As a powerful genomic "armament," cfDNA testing is available in multiple formats. Based on years of cumulative pathology experience, clinicians may select among whole-exome sequencing, whole-genome sequencing, targeted sequencing panels, and ultra-deep sequencing approaches [4]. The umbrella term next-generation sequencing (NGS) now encompasses these and related methodologies. Epigenetic profiling, including methylation-based [5] and phosphorylation-based sequencing [6], as well as ribosomal sequencing, further expands the scope of available testing technologies.

A recurring clinical difficulty centers on the fragile nature of RNA, which complicates molecular assessment and necessitates reliance on RNA sequencing to capture fusion events, alternative splicing, transcriptional profiles, and expression-level changes that DNA assays cannot detect [7]. An additional challenge emerges when clinicians attempt to quantify Minimal Residual Disease (MRD), which requires identifying exceedingly rare malignant cells within the bloodstream. Ultra-deep sequencing, capable of reaching depths of 10,000× or more, often provides the precision needed to detect these low-frequency variants [4], made possible by NGS.

Another complicating factor is germline noise, in which inherited variants obscure interpretation of somatic alterations. While many commercial platforms simply list these inherited findings as variants of uncertain significance, more advanced assays can compare tumor and normal samples directly to subtract germline interference [8].

Several commercial cfDNA platforms are now widely available and increasingly integrated into routine oncology care. These assays are particularly impactful for patients with advanced or metastatic disease where identifying actionable mutations or acquired drug resistance is essential. They are also gaining use in MRD assessment, including in conditions like chronic myeloid leukemia, and are being actively explored in metastatic and advanced colorectal cancer [9].

Patients who are responding well to treatment may inadvertently produce false-negative molecular test findings. This makes the timing of such evaluations critically important, especially when the disease burden is minimal or the patient is actively improving. In these settings, the scarcity of tumor cells releasing circulating tumor DNA (ctDNA) can mask the true molecular status and yield deceptively negative results.

Although tissue biopsy has long been the foundation for genomic characterization, it carries notable limitations: it is invasive, often cannot access intracranial lesions, and requires decalcification of osseous samples, which may

compromise molecular integrity. An additional—and major—obstacle is tumor heterogeneity across spatial locations and disease stages. For example, a lung malignancy that later spreads to the liver, adrenal glands, or brain may initially share the same driver mutation across all metastatic sites. Yet as each lesion evolves under different environmental pressures and responds differently to therapy, divergent mutational patterns can emerge [10]. This dynamic evolutionary process results in a patchwork of genomic diversity within the same patient.

Spatial separation itself also contributes to this heterogeneity. It is well-documented that metastatic lesions can display distinct histologic appearances, sometimes diverging substantially from the primary tumor. In colorectal cancer, for instance, hepatic metastases often show pathological characteristics that differ from the colorectal primary and may be less sensitive to pyrimidine–platinum-based chemotherapy, prompting consideration of localized interventions such as ablation, embolization, or radiation [11].

Clonal evolution further shapes this complexity. Tumors consist of multiple subclonal populations, some of which are therapy-resistant. These resistant populations typically do not arise spontaneously but emerge from pre-existing, slow-growing clones. During treatment, these resistant clones may expand while sensitive clones regress. A well-known example is non-small cell lung cancer treated with EGFR-targeted tyrosine kinase inhibitors (TKIs), where resistant clones can persist and rapidly proliferate once selective pressure changes [12].

One advantage of cell-free DNA (cfDNA) assays is their ability to integrate DNA shed from various tumor sites, offering a more representative snapshot of overall heterogeneity. However, they are not without limitations: lesions located within anatomical "sanctuaries," such as brain metastases, may shed minimal DNA into systemic circulation.

A wide array of commercial cfDNA tests exists, and their performance varies considerably depending on the design and sensitivity of the underlying gene panels. Minimal residual disease (MRD) testing generally falls under qualitative cfDNA analysis, whereas quantitative assays measure variables such as copy number changes or shifts in allele frequency, which are crucial for tracking acquired resistance or emerging mutations. Most clinical platforms incorporate components of both approaches.

Two essential designations in molecular diagnostics are “companion” and “complementary” tests. Companion diagnostics are mandated by the FDA to ensure that a particular therapy is used safely and effectively; a classic example is BRAF testing to determine eligibility for encorafenib in melanoma. Complementary tests, in contrast, provide useful guidance but are not required for drug prescribing.

A journey from mutation to action

Genomic test results play a central role in tailoring current and future treatment strategies. Clinical actionability refers to the use of a genetic alteration to guide decisions regarding drug selection, response prediction, toxicity risk, or clinical trial eligibility. In lung cancer, for instance, cfDNA assays are routinely used to identify acquired mutations that emerge after resistance to targeted therapies develops.

Gene polymorphisms affecting pharmacokinetics and pharmacodynamics

Dihydropyrimidine Dehydrogenase (DPyD) gene

The DPyD gene encodes the dihydropyrimidine dehydrogenase (DPD) enzyme, which is essential for metabolizing fluoropyrimidine chemotherapies—most notably 5-fluorouracil (5-FU) and capecitabine. Variants in this gene can reduce enzyme activity, thereby impairing drug breakdown and leading to elevated systemic exposure. This heightened exposure significantly increases the likelihood of severe or life-threatening fluoropyrimidine toxicities, making DPD genotyping an important tool for shaping safe and effective chemotherapy regimens. DPD also metabolizes tegafur, a 5-FU prodrug used outside the United States, with deficiency similarly predisposing patients to 5-FU–related toxicity [13].

Uridine Diphosphate Glucuronosyltransferase 1A1 (UGT1A1)

The UGT1A1 gene encodes an enzyme central to the glucuronidation of bilirubin and many xenobiotics. Variants such as **UGT1A128/28 or **UGT1A16/28 diminish enzyme function and can heighten toxicity from drugs that rely on this pathway—most notably govitecan, where reduced glucuronidation correlates with increased adverse effects [14]. The enzyme also influences the metabolism of agents such as irinotecan and etoposide, with reduced activity raising toxicity risk [15]. Some medications, such as enasidenib, act both as UGT1A1 substrates and inhibitors, and may cause hyperbilirubinemia through enzyme inhibition [16]. Because of these clinical

implications, understanding UGT1A1 variability is integral to individualized dosing and optimizing therapeutic safety.

O-6-Methylguanine–DNA Methyltransferase Gene (MGMT Gene)

The MGMT enzyme is a key participant in safeguarding genomic integrity by reversing alkylation-induced DNA damage. While this repair mechanism is essential for normal cellular homeostasis, its activity can undermine the therapeutic potency of alkylating chemotherapies such as temozolomide and dacarbazine, drugs broadly used in malignancies including brain tumors, sarcomas, and lymphomas. When tumor cells retain active MGMT, the cytotoxic effects of these agents diminish, leading to treatment resistance [17].

The predictive significance of MGMT promoter methylation was clearly demonstrated in the Stupp trial, where patients with methylated MGMT showed markedly improved survival after the addition of temozolomide to standard radiotherapy compared with unmethylated cases [18]. Long-term analyses have consistently validated the prognostic and predictive value of MGMT promoter methylation in glioblastoma, reinforcing its central role in forecasting sensitivity to alkylating agents [19].

Thiopurine S-Methyltransferase (TPMT) Gene

The TPMT gene codes for the TPMT enzyme, which modulates the metabolism of thiopurine medications—including azathioprine, 6-mercaptopurine, and thioguanine—through enzymatic methylation. Variants that diminish TPMT activity can dramatically alter the generation of active thiopurine metabolites, leading to excessive accumulation and heightened risk of myelosuppression and other toxicities. This drug–gene interaction illustrates the importance of incorporating pharmacogenomic principles into clinical practice, as patients with reduced TPMT activity require individualized dosing strategies and vigilant monitoring to balance efficacy with safety.

Cytochrome P450 (CYP) Isoenzymes

The CYP family comprises a diverse group of oxidative enzymes that constitute one of the major metabolic pathways for xenobiotics. Approximately 58 human CYP genes have been identified, each encoding enzymes with distinct but overlapping substrate specificities. CYP activity can be modified by environmental exposures—including drug–drug interactions that induce or inhibit enzymes such as CYP3A4, subsequently altering the metabolism of co-administered medications.

Pharmacogenomic research highlights the importance of CYP polymorphisms, which shape inter-individual and inter-ancestry differences in drug metabolism, generating phenotypes that range from ultra-rapid to poor metabolizers. Clinically relevant variability is especially pronounced in CYP2C9, CYP2C19, CYP2D6, and CYP3A4, which together metabolize the majority of commonly prescribed therapeutics [20].

Drug–gene interactions may involve several genes acting simultaneously. Irinotecan exemplifies such a polygenic model. Used extensively in malignancies such as lung, gastrointestinal, and ovarian cancers, irinotecan undergoes hepatic conversion to its active metabolite govitecan via carboxylesterases, while also being processed through CYP3A4-mediated oxidation into inactive metabolites, one of which can revert to govitecan after hydrolysis. When considering the combined effects of CYP3A4, UGT1A1 (discussed earlier), and carboxylesterase phenotypes, the resulting pharmacokinetic pathways become highly complex. Consequently, therapeutic adjustments must often be individualized based on patient-specific genetic profiles.

Polygenic risk scores

Decades of research have revealed a wide array of oncogenic mutations with therapeutic implications. Some, such as the RAS mutation family, required more than fifty years of investigation before becoming clinically targetable, whereas newer alterations like TET2 have only recently emerged as actionable candidates [21]. Others, such as TP53, remain challenging to directly target despite extensive study. Predicting which alterations will ultimately yield effective drug targets is exceedingly difficult.

To address this uncertainty, researchers increasingly evaluate combinations of mutations through polygenic risk scoring (PRS) approaches. By integrating multiple genomic signals, PRS may guide drug development and regulatory decisions. A successful example is olaparib, which received FDA approval for prostate cancer based on homologous recombination repair (HRR) gene mutations [22], and for ovarian cancer maintenance therapy using homologous recombination deficiency (HRD) profiling [23].

Another major breakthrough is the use of multigene panels, such as Oncotype DX, to assess chemotherapy benefit in early-stage estrogen receptor–positive, HER2-negative breast cancer. A cutoff score of 25 strongly predicts treatment response and is incorporated into NCCN guidelines. Similar multigenic prediction strategies are being explored for lung and colorectal cancers, with ongoing clinical trials aiming to extend these benefits across more tumor types.

Tumor resistance and genes

Tumor resistance emerges through a spectrum of molecular and cellular processes that enable malignant cells to evade therapeutic pressure. Mutations at drug-binding sites can diminish targeted drug affinity—for example, EGFR mutations that confer resistance to TKIs such as erlotinib, allowing tumor cells to continue proliferating. Cancer stem cells contribute further complexity by promoting tumor plasticity, enabling shifts in tumor histology under selective stress.

Moreover, reinforced DNA repair pathways, including homologous recombination (HR) and nucleotide excision repair (NER), can counteract therapy-induced damage and prevent apoptosis. Variations in gene expression, polymorphisms, and acquired mutations all play roles in shaping these resistance mechanisms. The following sections detail key examples of monogenic and polygenic contributions to therapeutic resistance.

Alternative pathways and off-target mutations

Cancer cells often evade therapy by diverting growth signals through backup molecular routes whenever a primary pathway is pharmacologically blocked. For example, sustained EGFR inhibition may prompt tumor cells to rely on alternative proliferative circuits such as HER2 or MET (mesenchymal-epithelial transition factor). In these settings, resistance may emerge through off-target mutations. Alterations affecting KRAS or BRAF are classic instances: even though the administered therapy does not directly target these genes, their mutations can drive downstream signaling cascades that override drug action, allowing continued cell survival and resistance.

ATP-binding cassette G2 subfamily (ABCG2) gene and efflux pump

Certain tumors develop resilience through increased drug export, mediated by efflux pumps that expel therapeutic agents from the intracellular space. One well-characterized protein involved in this mechanism is the breast cancer resistance protein (BCRP), which transports drugs such as methotrexate and topotecan [24]. BCRP—encoded by the ABCG2 gene—is expressed in tissues including the liver, kidney, gastrointestinal tract, and central nervous system. Growing attention has focused on ABCG2 polymorphisms [25] and on drug–drug interactions involving BCRP. Numerous inhibitors of this transporter have been identified [26], ranging from febuxostat and linezolid to lansoprazole, ketoconazole, and other benzimidazole derivatives [27, 28]. Because these interactions can influence systemic drug handling, BCRP is now recognized by the FDA as a key transporter with major implications for clinical pharmacokinetics.

Tumor microenvironment and polygenic score prediction

The Tumor Microenvironment (TME) encompasses the diverse cellular and structural components surrounding malignant cells—immune infiltrates, stromal elements, blood vessels, and extracellular matrix. This reciprocal and dynamic ecosystem shapes tumor progression and therapeutic responsiveness. For instance, in adrenal cortical carcinoma, immunotherapy tends to be ineffective due to features such as a low tumor mutational burden, extensive vascular supply, and absent or minimal PD-L1 expression. However, incorporating agents like lenvatinib or cabozantinib may reconfigure the TME, potentially increasing PD-L1 expression and improving responsiveness [29].

Tumors deploy multiple immunosuppressive mechanisms to block effective immune clearance. In head and neck squamous cell carcinoma (HNSCC), the TME exhibits potent immunosuppressive activity. Myeloid-derived suppressor cells (MDSCs) and macrophages operate interactively to amplify immune evasion, while regulatory T (Treg) cells contribute by suppressing CD4+ T-cell proliferation and inducing apoptosis of CD8+ T cells [30].

Biomarker development targeting the TME has focused on solid tumors such as triple-negative breast cancer, ovarian cancer, metastatic melanoma, mixed solid tumors, and head and neck cancers. A notable investigational biomarker is VIGex, a 12-gene expression profile capturing immune-activating and immune-suppressive signatures, including CTLA-4 and CD274 (PD-L1). In the INSPIRE trial, the VIGex HOT score correlated strongly with improved progression-free and overall survival [31].

Genetic alterations, drug targets, and tumor-agnostic approvals

Tumor-agnostic approvals represent a landmark transition in cancer therapeutics, reframing treatment selection around molecular features rather than tissue of origin. These approvals hinge on the presence of actionable genetic markers that span different cancers, such as tumor mutational burden (TMB), mismatch repair (MMR) deficiency, microsatellite instability (MSI), neurotrophic tyrosine receptor kinase (NTRK) fusions, rearranged during transfection (RET) fusions, and rapidly accelerated fibrosarcoma B-type (BRAF) mutations. By directly targeting these molecular drivers, clinicians can offer personalized treatments that operate independently of where the tumor began, broadening therapeutic options and potentially enhancing outcomes.

This paradigm shift has cemented precision oncology as a core approach in modern cancer care, with FDA-approved agents corresponding to major tumor-agnostic biomarkers including TMB, dMMR, MSI, NTRK fusion, RET fusion, and BRAF alterations.

MMR/MSI

Evaluating MMR/MSI status yields vital information regarding a tumor's immunogenic profile and likelihood of responding to immunotherapy, thereby shaping therapeutic choices. In this rapidly evolving field, ongoing discussions highlight potential forthcoming innovations. Among currently available options, pembrolizumab has established itself as a pioneering therapy for MSI-high solid tumors **(Table 1)**, alongside dostarlimab. Nivolumab—alone or in combination with ipilimumab—is included in the NCCN guidelines for MSI-high solid tumors, as reflected in the December 2024 NCCN compendium.

Table 1. Pembrolizumab agnostic approvals and specific diagnostic requirements.

Pembrolizumab agnostic approval	Testing suggested	Diagnostic requirement
Tumor mutational burden	Next-generation sequencing (NGS)	≥10[a]
Mismatch repair	Immunohistochemistry (IHC)	Deficient
Microsatellite instability	Polymerase chain reaction (PCR)/NGS	High
POLE/*POLD1*[b]	PCR/NGS	Mutated
PD-L1[c]	Immunohistochemistry	≥50

aThis cut-off value is approved with tissue biopsy.

bThis NCCN endorsement is for colorectal cancer, small bowel cancer, and appendiceal cancer.

cThis indication was authorized in certain countries; Contraindications to pembrolizumab should be screened before prescribing. PD-L1 (programmed death ligand 1).

Patients exhibiting deficient MMR or MSI-high profiles generally share overlapping biological features. Nevertheless, occasional discordance may arise—most notably between endometrial and colorectal cancers—largely due to differing frequencies of germline variants in lower-penetrance genes such as MSH6 (MutS Homolog 6) and PMS2 (postmeiotic segregation increased 2) [32]. Despite these exceptions, immunohistochemistry (IHC) findings indicating loss of MMR function typically align with MSI-high status, and the reverse is usually true. While colorectal and endometrial cancers represent the primary tumor types in which these abnormalities are detected, they also appear, albeit at reduced rates, in malignancies such as prostate cancer (~3%) and gastric cancer.

Tumor mutational burden (TMB)

TMB reflects the number of non-synonymous mutations within a tumor genome and can signal the presence of neo-antigens capable of provoking an immune response. Although a higher TMB generally corresponds with enhanced responsiveness to immunotherapy across numerous cancer types, notable exceptions—such as primary gliomas—exist [33]. Pembrolizumab received FDA approval following the KEYNOTE-158 trial, which demonstrated clinical benefit in tumors exhibiting at least 10 mutations per megabase (mut/Mb) [34]. A threshold of ≥10 mut/Mb is widely considered actionable when derived from tissue-based assays **(Table 1)**. However, whether cell-free DNA (cfDNA) assays require a higher cutoff remains unresolved, and ongoing studies continue to evaluate the validity of cfDNA-based TMB estimation [35]. By adopting tumor-agnostic frameworks, the field continues to advance toward more individualized oncology care, offering broader therapeutic prospects and improved patient quality of life.

BRAF

Detecting BRAF mutations enables the use of molecularly targeted therapies designed to block aberrant MAPK pathway signaling. Several tyrosine kinase inhibitors are now approved for this purpose. Dabrafenib in combination with trametinib is authorized for tumors harboring BRAF V600E mutations, including glioblastoma and biliary tract cancers [36, 37]. These approvals stem from strong evidence observed across diverse malignancies, which ultimately supported a tumor-agnostic indication (NCI. BRAF; Winstead, 2022 [38]). Notably, this therapeutic combination has also appeared in reports involving certain non-V600E BRAF variants, used off-label in small studies and case reports [39].

NTRK fusion

Larotrectinib was the first agent authorized for cancers driven by activating NTRK fusions, including pediatric tumors. Targeting these rearrangements with tyrosine kinase inhibitors such as entrectinib has yielded striking responses across a broad spectrum of malignancies [40]. Larotrectinib's approval marked the first tissue-agnostic authorization for tumors with NTRK fusions, demonstrating activity in multiple settings including salivary gland malignancies and soft-tissue sarcomas [41]. On 13 June 2024, the FDA granted accelerated approval to repotrectinib for tumor-agnostic treatment of NTRK fusions [42]. Entrectinib and repotrectinib also inhibit ROS1, and both agents are licensed for ROS1-mutated non-small cell lung cancer; however, this indication does not fall under the tumor-agnostic category.

RET fusion

Selpercatnib, developed for malignancies harboring RET-activating fusions, has demonstrated meaningful activity in medullary thyroid cancer and other solid tumors expressing these alterations. Findings from the Libretto trial supported its approval. Such tumor-agnostic authorizations illustrate the expanding role of precision oncology, where therapeutic selection is driven by molecular alterations rather than tissue-specific histopathologic classification [43].

Isocitrate dehydrogenase gene (IDH)

Mutations in IDH1 and IDH2 arise across several cancers—including gliomas and acute myeloid leukemia (AML)—and generate a neomorphic enzymatic activity that leads to accumulation of the oncometabolite 2-hydroxyglutarate (2-HG). Elevated 2-HG perturbs cellular function through mechanisms such as epigenetic dysregulation, thereby contributing to tumorigenesis. Small-molecule inhibitors targeting mutant IDH enzymes, including ivosidenib and enasidenib, have emerged as effective therapies in IDH-mutated malignancies. Their ability to suppress 2-HG production and partially restore normal cellular processes has resulted in FDA approvals based on clinical success in relapsed or refractory AML and glioma populations.

A more recent FDA approval includes vorasidenib, which demonstrates benefit in select low-grade gliomas (NCI. IDH; Winstead, 2023 [44]). Additionally, olutasidenib, a selective IDH1 inhibitor, has shown durable remission, transfusion independence, and overall strong clinical responses in relapsed or refractory IDH1-mut AML, leading to its approval for this indication [45].

Human Epidermal Growth Factor Receptor 2 (HER2)

The rapid expansion of the tissue-agnostic therapeutic arena has been further propelled by recent developments surrounding trastuzumab deruxtecan, which has emerged as a contender for a tumor-agnostic label—an advancement that highlights ongoing momentum in therapeutic innovation [46]. The FDA granted this agent priority review on 30 January 2024 for adults with HER2-positive solid tumors who had either received prior therapy or lacked remaining treatment options, and full approval followed on 5 April 2024. This authorization represents a landmark achievement: it is the first antibody–drug conjugate (ADC) to secure a tumor-agnostic indication, and simultaneously the first HER2-targeted therapy permitted for use across a broad spectrum of malignancies. The approved indication includes patients with unresectable or metastatic HER2+ disease exhibiting immunohistochemistry (IHC) 3+ expression.

Results and Discussion

When clinicians interpret pathological findings in breast cancer, the marked heterogeneity of tissue samples—along with inconsistent analytical readouts—has long generated uncertainty, particularly in cases categorized as HER2 equivocal. Similar discrepancies have also been noted in cfDNA assessments processed across different laboratories, where methodological variability has produced inter-center inconsistencies. Standardizing procedures and establishing universally accepted operational guidelines is therefore essential, regardless of whether testing is performed in accredited facilities or on-site institutional units. Because genetic results form the foundation of precision-based therapeutic strategies, any inaccuracy at this earliest step can propagate significant downstream consequences.

Evidence from real-world genomic assays frequently reveals that a single sample may harbor numerous gene alterations. While non-actionable variants generally lack therapeutic relevance, actionable alterations can direct the use of targeted therapies supported by mechanistic or clinical evidence. Complexity arises when more than one actionable mutation appears concurrently, forcing clinicians to prioritize among multiple potential therapeutic targets. Such decisions often require individualized evaluation, balancing expected efficacy, safety considerations, and cost-effectiveness.

The implementation of pharmacogenomics in clinical practice varies substantially between countries, despite international clinicians often referencing the same data presented at global scientific meetings. This disparity complicates the management of patients who seek care across borders. Besides linguistic and cultural barriers, challenges also stem from healthcare expenditures, inconsistent datasets, and differing regulatory frameworks.

China's National Medical Products Administration (NMPA) has authorized nearly a dozen PD-1 monoclonal antibodies, many of which are used widely as more affordable alternatives to FDA-approved agents like pembrolizumab or nivolumab. However, these NMPA-approved drugs have not yet obtained FDA approval. This raises an important clinical question: when such PD-1 inhibitors are administered to patients with MSI-H or high TMB—settings in which pembrolizumab has demonstrated clear benefit—are outcomes compromised due to a lack of equivalent clinical evidence? The logical, though time-intensive, solution would be the initiation of dedicated clinical trials evaluating these agents in MSI-H cohorts, which is ultimately the direction anticipated.

Pharmacogenomic application becomes even more challenging when repeated testing yields inconsistent results. One practical option is rebiopsy for updated molecular profiling. For instance, patients with recurrent estrogen receptor-positive breast cancer may be considered for treatment with elacestrant if an ESR1 mutation is identified. Alternatively, clinicians may adopt a polygenic strategy; alterations in PI3K, PTEN, or AKT may steer therapeutic decisions toward different targeted pathways. There is rarely a straightforward answer, as optimal management requires a detailed appraisal of co-occurring mutations and numerous patient-specific factors. Overall, pharmacogenomic practice is most effective when integrated within a multidisciplinary framework that can collectively address these evolving complexities.

Current pharmacogenomic tools already provide powerful support for tailoring therapies to individual patients. Additional resources may help mitigate existing challenges, and clinical research continues to be one of the most influential assets in oncology. Patients with NTRK fusions, for example, may be eligible for ongoing repotrectinib trials when the drug is not yet available on formulary. Likewise, those who have exhausted commercial KRAS-targeted options might enroll in clinical studies evaluating emerging pan-RAS inhibitors. Through such strategies—combining pharmacogenomic insight with well-designed research opportunities—the field of precision medicine will advance to a more sophisticated and impactful stage, ultimately enhancing both patient outcomes and the broader standards of oncologic care.

Conclusion

The landscape of pharmacogenomics and precision medicine is advancing at an extraordinary pace, propelled by breakthroughs in sequencing platforms, refined molecular testing techniques, and a growing armamentarium of targeted therapies. Incorporating genomic data into everyday clinical decision-making has reshaped modern oncology, allowing clinicians to pinpoint clinically actionable alterations and tailor interventions to the unique molecular features of each patient. The emergence of tumor-agnostic indications reflects a major conceptual transition, enabling the application of targeted agents across multiple malignancies solely on the basis of shared genomic biomarkers. Within this framework, pharmacogenetic testing remains an indispensable component of personalized care, informing the most suitable drugs and individualized dosing strategies to enhance efficacy and reduce avoidable toxicity. As precision medicine continues to mature, sustained scientific progress and

technological innovation will deepen our insight into tumor behavior and therapeutic responsiveness, ultimately driving more effective treatment pathways and elevating the overall well-being and prognosis of individuals living with cancer.

Acknowledgments: The authors acknowledge and express appreciation to pharmacy colleagues who work at Putian University Affiliated Hospital for providing translation on certain foreign-approved drugs.

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Chakravarty D, Johnson A, Sklar J, Lindeman NI, Moore K, Ganesan S, et al. Somatic genomic testing in patients with metastatic or advanced cancer: ASCO provisional clinical opinion. J Clin Oncol. 2022;40(11):1231–58. doi:10.1200/JCO.21.02767
2. Li Y, Meng L, Ma Y, Li Y, Xing X, Guo C, et al. Determination of osimertinib, aumolertinib, and furmonertinib in human plasma for therapeutic drug monitoring by UPLC-MS/MS. Molecules. 2022;27(14):4474. doi:10.3390/molecules27144474
3. Dean L, Kane M. Capecitabine therapy and DPYD genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, eds. Medical Genet Summaries. Bethesda (MD); 2012.
4. van Dessel LF, Vitale SR, Helmijr JCA, Wilting SM, van der Vlugt-Daane M, Oomen-de Hoop E, et al. High-throughput isolation of circulating tumor DNA: a comparison of automated platforms. Mol Oncol. 2019;13(2):392–402. doi:10.1002/1878-0261.12415
5. Rauluseviciute I, Drablos F, Rye MB. DNA methylation data by sequencing: experimental approaches and recommendations for tools and pipelines for data analysis. Clin Epigenet. 2019;11(1):193. doi:10.1186/s13148-019-0795-x
6. Yu J, Li Y, Li Y, Liu X, Huo Q, Wu N, et al. Phosphorylation of FOXN3 by NEK6 promotes pulmonary fibrosis through Smad signaling. Nat Commun. 2025;16(1):1865. doi:10.1038/s41467-025-56922-7
7. Kukurba KR, Montgomery SB. RNA sequencing and analysis. Cold Spring Harb Protoc. 2015;(11):951–69. doi:10.1101/pdb.top084970
8. Koboldt DC, Steinberg KM, Larson DE, Wilson RK, Mardis ER. The next-generation sequencing revolution and its impact on genomics. Cell. 2013;155(1):27–38. doi:10.1016/j.cell.2013.09.006
9. Jacome AA, Johnson B. Minimal residual disease in colorectal cancer: are we finding the needle in a haystack? Cells. 2023;12(7):1068. doi:10.3390/cells12071068
10. de Visser KE, Joyce JA. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth. Cancer Cell. 2023;41(3):374–403. doi:10.1016/j.ccell.2023.02.016
11. Halama N, Spille A, Lerchl T, Brand K, Herpel E, Welte S, et al. Hepatic metastases of colorectal cancer are rather homogeneous but differ from primary lesions in terms of immune cell infiltration. Oncoimmunology. 2013;2(4):e24116. doi:10.4161/onci.24116
12. Roper N, Brown AL, Wei JS, Pack S, Trindade C, Kim C, et al. Clonal evolution and heterogeneity of osimertinib acquired resistance mechanisms in EGFR mutant lung cancer. Cell Rep Med. 2020;1(1):100007. doi:10.1016/j.xcrm.2020.100007
13. Leung JS. Adjuvant S-1 chemotherapy after curative resection of gastric cancer. Hong Kong Med J. 2017;23(3):315. doi:10.12809/hkmj176283
14. Rozenblit M, Lustberg MB. Sacituzumab govitecan: ascending the treatment algorithm in triple negative breast cancer. Ann Transl Med. 2022;10(7):390. doi:10.21037/atm-22-484
15. Negoro Y, Yano R, Yoshimura M, Suehiro Y, Yamashita S, Kodawara T, et al. Influence of UGT1A1 polymorphism on etoposide plus platinum-induced neutropenia in Japanese patients with small-cell lung cancer. Int J Clin Oncol. 2019;24(3):256–61. doi:10.1007/s10147-018-1358-4

16. DiNardo CD, Venugopal S, Lachowiez C, Takahashi K, Loghavi S, Montalban-Bravo G, et al. Targeted therapy with the mutant IDH2 inhibitor enasidenib for high-risk IDH2-mutant myelodysplastic syndrome. Blood Adv. 2023;7(11):2378–87. doi:10.1182/bloodadvances.2022008378
17. Wu S, Li X, Gao F, de Groot JF, Koul D, Yung WKA. PARP-mediated PARylation of MGMT is critical to promote repair of temozolomide-induced O6-methylguanine DNA damage in glioblastoma. Neuro Oncol. 2021;23(6):920–31. doi:10.1093/neuonc/noab003
18. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352(10):997–1003. doi:10.1056/NEJMoa043331
19. Chen L, Wen A. Unveiling the role of O(6)-methylguanine-DNA methyltransferase in cancer therapy: insights into alkylators, pharmacogenomics, and others. Front Oncol. 2024;14:1424797. doi:10.3389/fonc.2024.1424797
20. von Moltke LL, Greenblatt DJ, Grassi JM, Granda BW, Venkatakrishnan K, Schmider J, et al. Multiple human cytochromes contribute to biotransformation of dextromethorphan in-vitro: role of CYP2C9, CYP2C19, CYP2D6, and CYP3A. J Pharm Pharmacol. 1998;50(9):997–1004. doi:10.1111/j.2042-7158.1998.tb06914.x
21. Zou Z, Dou X, Li Y, Zhang Z, Wang J, Gao B, et al. RNA m5C oxidation by TET2 regulates chromatin state and leukaemogenesis. Nature. 2024;634(8035):986–94. doi:10.1038/s41586-024-07969-x
22. Scott RJ, Mehta A, Macedo GS, Borisov PS, Kanesvaran R, El Metnawy W. Genetic testing for homologous recombination repair (HRR) in metastatic castration-resistant prostate cancer (mCRPC): challenges and solutions. Oncotarget. 2021;12(16):1600–14. doi:10.18632/oncotarget.28015
23. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. Cancer Discov. 2015;5(11):1137–54. doi:10.1158/2159-8290.CD-15-0714
24. U.S. Food and Drug Administration. Label for [drug] [Internet]. 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205436s005lbl.pdf
25. Heyes N, Kapoor P, Kerr ID. Polymorphisms of the multidrug pump ABCG2: a systematic review of their effect on protein expression, function, and drug pharmacokinetics. Drug Metab Dispos. 2018;46(12):1886–99. doi:10.1124/dmd.118.083030
26. Mao Q, Unadkat JD. Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport—an update. AAPS J. 2015;17(1):65–82. doi:10.1208/s12248-014-9668-6
27. Breedveld P, Zelcer N, Pluim D, Sonmezer O, Tibben MM, Beijnen JH, et al. Mechanism of the pharmacokinetic interaction between methotrexate and benzimidazoles: potential role for breast cancer resistance protein in clinical drug-drug interactions. Cancer Res. 2004;64(16):5804–11. doi:10.1158/0008-5472.CAN-03-4062
28. Ikemura K, Hiramatsu SI, Shinogi Y, Nakatani Y, Tawara I, Iwamoto T, et al. Concomitant febuxostat enhances methotrexate-induced hepatotoxicity by inhibiting breast cancer resistance protein. Sci Rep. 2019;9(1):20359. doi:10.1038/s41598-019-56900-2
29. Bedrose S, Miller KC, Altameemi L, Ali MS, Nassar S, Garg N, et al. Combined lenvatinib and pembrolizumab as salvage therapy in advanced adrenal cortical carcinoma. J Immunother Cancer. 2020;8(2):e001009. doi:10.1136/jitc-2020-001009
30. Wang HC, Chan LP, Cho SF. Targeting the immune microenvironment in the treatment of head and neck squamous cell carcinoma. Front Oncol. 2019;9:1084. doi:10.3389/fonc.2019.01084
31. Hernando-Calvo A, Yang SYC, Vila-Casadesus M, Han M, Liu ZA, Berman AHK, et al. Combined transcriptome and circulating tumor DNA longitudinal biomarker analysis associates with clinical outcomes in advanced solid tumors treated with pembrolizumab. JCO Precis Oncol. 2024;8:e2400100. doi:10.1200/PO.24.00100
32. Kim YN, Kim MK, Lee YJ, Lee Y, Sohn JY, Lee JY, et al. Identification of Lynch syndrome in patients with endometrial cancer based on a germline next generation sequencing multigene panel test. Cancers (Basel). 2022;14(14):3406. doi:10.3390/cancers14143406
33. Khasraw M, Walsh KM, Heimberger AB, Ashley DM. What is the burden of proof for tumor mutational burden in gliomas? Neuro Oncol. 2020;23(1):17–22. doi:10.1093/neuonc/noaa256

34. Cristescu R, Aurora-Garg D, Albright A, Xu L, Liu XQ, Loboda A, et al. Tumor mutational burden predicts the efficacy of pembrolizumab monotherapy: a pan-tumor retrospective analysis of participants with advanced solid tumors. J Immunother Cancer. 2022;10(1):e003091. doi:10.1136/jitc-2021-003091
35. Krizova L, Safarikova M, Kalousova M, Pfeiferova L, Kubena AA, Vocka M, et al. New methodology of TMB assessment from tissue and liquid biopsy in NSCLC. PLoS One. 2022;17(9):e0275121. doi:10.1371/journal.pone.0275121
36. Subbiah V, Lassen U, Elez E, Italiano A, Curigliano G, Javle M, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 2020;21(9):1234–43. doi:10.1016/S1470-2045(20)30321-1
37. Wen PY, Stein A, van den Bent M, De Greve J, Wick A, de Vos F, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol. 2022;23(1):53–64. doi:10.1016/S1470-2045(21)00578-7
38. Winstead E. Dabrafenib–trametinib combination approved for solid tumors with BRAF mutations [Internet]. 2022. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-dabrafenib-trametinib-braf-solid-tumors
39. Shimoi T, Sunami K, Tahara M, Nishiwaki S, Tanaka S, Baba E, et al. Dabrafenib and trametinib administration in patients with BRAF V600E/R or non-V600 BRAF mutated advanced solid tumours (BELIEVE, NCCH1901): a multicentre, open-label, and single-arm phase II trial. EClinicalMedicine. 2024;69:102447. doi:10.1016/j.eclinm.2024.102447
40. Manea CA, Badiu DC, Ploscaru IC, Zgura A, Bacinschi X, Smarandache CG, et al. A review of NTRK fusions in cancer. Ann Med Surg (Lond). 2022;79:103893. doi:10.1016/j.amsu.2022.103893
41. Iannantuono GM, Riondino S, Sganga S, Rosenfeld R, Guerriero S, Carlucci M, et al. NTRK gene fusions in solid tumors and TRK inhibitors: a systematic review of case reports and case series. J Pers Med. 2022;12(11):1819. doi:10.3390/jpm12111819
42. U.S. Food and Drug Administration. FDA grants accelerated approval to repotrectinib for adult and pediatric patients with NTRK gene fusion-positive solid tumors [Internet]. 2024. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-repotrectinib-adult-and-pediatric-patients-ntrk-gene-fusion-positive
43. Winstead E. Selpercatinib slows progression of RET-positive lung, medullary thyroid cancers [Internet]. 2023. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2023/selpercatinib-ret-lung-medullary-thyroid
44. Winstead E. Vorasidenib treatment shows promise for some low-grade gliomas [Internet]. 2023. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2023/vorasidenib-low-grade-glioma-idh-mutations
45. Venugopal S, Watts J. Olutasidenib: from bench to bedside. Blood Adv. 2023;7(16):4358–65. doi:10.1182/bloodadvances.2023009854
46. Jorgensen JT. The potential of trastuzumab deruxtecan as a tissue agnostic drug. Oncology. 2023;101(12):836–42. doi:10.1159/000533866