Online at: https://researchtrendsjournal.com
Indexed Journal

ISSN No: 2584-282X
Peer Reviewed Journal

INTERNATIONAL JOURNAL OF TRENDS IN EMERGING RESEARCH AND DEVELOPMENT

Volume 3; Issue 4; 2025; Page No. 411-417

Received: 07-04-2025
Accepted: 13-05-2025
Published: 05-07-2025

The Pharmacogenomic Role of The Immune System Genetics and of Previously Neglected Rare Genetic Variants

[1]Suneel Kumar Yadav, [2]Dr. Jitender K Malik, [3]Dr. Vivek Gupta and [4]Dr. Deepak Jhariya

[1]Research Scholar, PK University, Shivpuri, Madhya Pradesh, India
[2-4]Professor, Department of Pharmacy, PK University, Shivpuri, Madhya Pradesh, India

DOI: https://doi.org/10.5281/zenodo.20381947

Corresponding Author: Suneel Kumar Yadav

Abstract

This review discusses the advancements and challenges in personalized medicine, with a particular focus on pharmacogenomics, which tailors drug therapies to individual genetic profiles. Personalized healthcare utilizes various personal traits-such as age, sex, and socioeconomic status-to enhance disease prevention and treatment. Recent developments in genomics have improved the ability to customize medications for specific patient categories or individuals. The review emphasizes the importance of understanding both the patient's and tumor's genomes in cancer treatment, as this knowledge can optimize drug selection and dosage, potentially reducing side effects compared to traditional chemotherapy. Despite the promise of pharmacogenomic testing, its widespread adoption faces barriers, including financial constraints and insurance coverage issues. The review advocates for preemptive pharmacogenomic testing, which can be more cost-effective and beneficial over a patient's lifetime, and suggests integrating these findings into electronic health records to maximize clinical utility.

Keywords: Treatment, Pharmacogenomics, Anti-cancer, Imatinib, Haplotypes, Patients', Drugs, Genotype

Introduction

Studies investigating the potential of pharmacogenomics and pharmacogenetics in cancer treatment have proliferated in response to this renewed interest. One definition of PGx is the study of hereditary variables that may impact pharmacological efficacy. In this context, genetic factors might include things like chromosomal changes, Haplotypes, CNVs, or changes in copy number, and SNPs, or variations in single nucleotide positions, are components of DNA. Treatment options based on the idea that specific genes significantly impact medication sensitivity and the development of genome-wide approaches hence depended on investigating potential genetic variations significant in drug response. To better understand individual patients' prognoses, forecast treatment results, and increase the effectiveness and safety of drugs, it is crucial to investigate and uncover drug sensitivity may be influenced by both somatic and germline genetic factors. Another potential outcome of PGx techniques that include a more thorough knowledge of genetic and molecular processes is the discovery of novel, safer, and more effective molecularly targeted medicines for tumor patients. To enhance effectiveness and limit harm, anti-cancer treatment regimens may be personalized to each patient's genotype.

Given the considerable toxicities caused by the nonspecific effects of cytotoxic chemotherapeutic drugs and their limited therapeutic index, PGx methods were deemed very relevant for these regimens. However, few studies have focused on studying the PGx of targeted medicines because to the fact that these treatments target genes or proteins unique to cancer cells. Patients who do not react, develop resistance, or have negative medication reactions highlight the significance of PGx of targeted treatments. This phenomenon is shown, for instance, by the fact that extra genetic variables must be taken into account when choosing medications for in individuals with chronic myeloid leukemia (CML), the tyrosine kinase inhibitor (TKI) imatinib does not work. Since imatinib was unable to

provide a full cytogenetic response in one-third of CML patients treated with it, studying the PGx of targeted medicines is of the utmost importance. develop resistance to the drug.

Treatment A full Between fifty percent and eighty percent of patients who had chemotherapy with busulfan and hydroxyurea showed a hematological response, defined as a complete blood count (CHR) of twelve thousand or less white cells per deciliter (42,000/µl). individuals with CP-CML before the advent of targeted treatment. It was unusual to have a full remission of cytogenetic markers (CCyR: absence of Ph+ cells). Complete hematologic and cytogenetic responses were more often achieved with the later implementation of interferon-α treatment, a human cytokine. Imatinib mesylate, a When it came to treating chronic myeloid leukemia (CML), the BCR-ABL1 inhibitor-which was approved by the US FDA in 2001-far outperformed all previous treatments in the IRIS trial. It achieved CHR in 95% of patients and CCyR in 76%. From 31% in the early 1990s to 66% in 2012, there was a substantial rise in the 5-year survival rates for CP-CML.in that time. thanks to the advent of imatinib as frontline treatment.

Unsatisfactory treatment result was the reason given for 16% of patient withdrawals About 55% of patients continued taking imatinib throughout the research that followed the first IRIS experiment over eight years. Imatinib resistance was often generated by point mutations in the BCR-ABL1 oncogene's kinase domain. To combat this, second-generation TKIs were introduced, such as nilotinib and dasatinib, which exhibited a much stronger affinity to BCR-ABL1 than imatinib. Patients with chronic myeloid leukemia who had developed a resistance to imatinib benefited greatly from these drugs. In patients recently diagnosed with CP-CML, the goal was to achieve CCyR and a major molecular response (MMR) within 12 months, which is defined as a BCR-ABL1 RNA level less than 0.1% on the International Scale., the second generation of TKIs fared better than imatinib. hence, they were authorized as first-line treatments. When looking at resistant instances, BCR-ABL1 point mutations only explain about half of them. Some of the reported adverse effects include physical and mental health difficulties, as well as poor functionality, pain, energy, social functioning, and limits in one's position as a result of emotional issues. by patients as a result of drug intolerance or cytotoxicity, which emphasizes the significance of PGx in targeted therapies.

Literature Review

Barratt *et al*. (2017) [1] Chronic myeloid leukaemia (CML) was first treated molecularly with imatinib, the pioneer about tyrosine kinase inhibitors and therapeutic applications of these compounds. Among the most popular first-line therapies for CML, it has expanded its indications to include a wide range of BCR-ABL, c-KIT, and PDGFR-driven malignancies. Because of its intracellular site of action and low hepatic extraction ratio, the liver removes the majority of imatinib after oral administration. It binds to plasma proteins with an affinity of 95%. It is yet unclear if pharmacogenomic data may supplement targeted concentration intervention or therapeutic medication monitoring for imatinib. If we want better tools for individualized imatinib dose and a better mechanistic knowledge of the variables controlling varied intracellular distribution of imatinib and its association to response, we need better research designs.

Ankathil *et al*. (2018) [2] Resistance developing in a significant portion recipients of imatinib mesylate for the treatment of chronic myeloid leukemia (CML) (IM) therapy has emerged as a significant concern in clinical practice, despite the drug's great effectiveness and better clinical results. Multiple cohort studies have examined IM prognosis and treatment responsiveness in relation to pharmacogenetic variations. Nevertheless, this investigation has yielded results that are somewhat contradictory. For patients with chronic myeloid leukemia (CML), this is the most up-to-date depiction of how pharmacogenetic variability affects the effectiveness of IM therapy. this study.

Singh *et al*. (2019) [3] Thanks to recent developments in pharmacogenomics, we can now understand why various drugs have varied effects. The foundation for suggesting a treatment and its dosage to a specific patient is the learning about genetic variants and how they relate to the drug's varying effects. The results of therapies are improved and the danger of toxicity and other side consequences is reduced when therapy is prescribed, designed, and implemented based on genetic composition. The current method of therapy, which relies on trial and error, will be replaced by a more precise knowledge of how individual variances impact medication response, metabolism, excretion, and toxicity. When it comes to individualized treatment, there are a lot of roadblocks. Accelerating genetically-based therapeutic customization is possible with the help of future developments in genetics, diagnostic methods, data analysis, clinical decision-making, and a viable commercial strategy.

Nimra *et al*. (2023) [4] The identification and treatment of leukemia, a complex group of blood malignancies, remain formidable obstacles. New opportunities for customizing treatment plans to each patient's distinct genetic and molecular traits have emerged as a result of recent developments in pharmacogenomics. Drug metabolism, effectiveness, and the likelihood of side effects are all affected by genetic variations in leukemia. The TPMT variation, which affects thiopurine therapy in ALL, the UGT1A1 polymorphism, which affects irinotecan toxicity in AML, and the SLCO1B1 variant, which affects methotrexate response in ALL, are all notable instances. By zeroing in on particular genetic mutations, targeted treatments have completely transformed the way leukemia is treated. This article summarizes the current state of pharmacogenomics in leukemia by outlining important results and trends. Improving outcomes and survivability is anticipated via the use of combination medicines, the identification of biomarkers, and patient-centric care.

Zaker *et al*. (2023) [5] Prior knowledge as a targeted treatment, in order to identify those individuals most likely to suffer from cardiotoxicity when administered anthracyclines., even though imatinib has great effectiveness and increased clinical response levels. Because of these large individual differences in response, studying the pharmacogenetics of cancer medications has become an increasingly pressing issue. Efflux and influx transporters, BCR-ABL point mutations, and other variables are

examined in this review in relation to their impact about the responsiveness of targeted medications in chronic myeloid leukemia. Another area that we prioritize is the ways in which patients might conquer these challenges.

Pharmacogenomics on Imatinib

One common treatment for chronic myeloid leukemia (CML) is the competitive tyrosine kinase inhibitor imatinib mesylate. inhibitor. Other conditions linked to PDGFR gene rearrangement that have showed improvement in treatment include c-KIT mastocytosis, myeloproliferative disorders, and advanced gastrointestinal stromal tumors (GISTs). In IM inhibits the tyrosine kinase activity of the fusion protein BCR-ABL in chronic myeloid leukemia (CML). This protein is involved in leukemogenesis and is produced by a t (9;22) (q34, q11) translocation on the Philadelphia chromosome. The binding of IM to the ABL kinase domain, it takes up residence in the ATP-binding pocket. This stops the protein from changing its conformation and becoming active, which in turn causes target cells to die.

A When the Philadelphia chromosome is not present in bone marrow metaphase analysis, it is referred to as CCyR, or a full cytogenetic response. Normal peripheral blood counts and spleen counts suggest complete hematological remission. When levels of BCR-ABL transcript drop, it is called a massive molecular response (MMR). that is one thousand times smaller than the standardized baseline, measured in log units. The effectiveness of CML therapy is assessed using these three parameters. Table indicates other possible cytogenetic or molecular response levels. Some individuals do not meet response criteria, even though IM has excellent success in treating chronic phase CML. For instance, around At 18 months, 25% of patients still hadn't achieved CCyR. while another 25% of patients who reacted well initially developed resistance down the road. In addition to medication interactions, incorrect dosage, and treatment non-compliance, mutations or amplification of the target protein, downstream pathways that are not dependent on drug-resistant BCR-ABL Absorption, transport, metabolism, and excretion are four pharmacokinetic features that may impact resistance development. Aside from CML, IM blocks the tyrosine kinase domains of KIT and PDGFRα/Y in different types of cancer. Chronic eosinophilic leukemia, a myeloproliferative condition caused by a PDGFR rearrangement (a fusion transcript of FIP1-like1 and PDGFRA), is often treated with a lower dosage of IM due to its high sensitivity to the treatment. Patients with mastocytosis had an overall response rate of 18% to 36% if their c-KIT mutation status is known. With a 50% to 70% response rate and a 70% overall survival percentage after 2 years, achieved in GISTs with IM.

Both There is a fourfold variation across patients within the standard dose range in terms of systemic exposure at a certain dose and the dosage needed to achieve a particular objective level. Changing the dosage of a cancer drug might have unintended consequences, such as increased toxicity or a lack of anticancer activity. On the other hand, you can get rashes, nausea, mild edema, muscular cramps, and neutropenia. most often reported adverse reactions following intramuscular (IM) medication administration; lower drug exposure has been associated with decreased IM effectiveness. For those afflicted with CML, the trough intramuscular plasma levels (Cmin) after a typical medication dosage have been linked to MMR. The most sensitive and specific plasma threshold for predicting MMR was 1,002 ng/ml. Compared to patients with Cmin levels above this threshold, those with Cmin levels below it had a lower likelihood of achieving MMR. Similarly, Individuals exhibiting advanced GISTs and a Cmin level over 1,100 ng/ml had a better prognosis and a longer time to progression when their circulating IM levels were higher. response rate.

There may be a hereditary component to the observed variation in pharmacokinetics between individuals. An individual's bioavailability-the degree to which a medicine reaches the bloodstream-may be impacted by genetic variations in genes associated with transport, metabolism, and elimination from the body via the musculoskeletal system. The oral bioavailability of a pharmaceutical is defined as the amount of the drug that enters the circulation after it has passed through the digestive system. Alpha-1 acid glycoprotein (AGP) and serum albumin are the primary plasma proteins that bind about 95% of IM in humans. Breast cancer resistance protein (BCRP) and the P glycoprotein (P-gp, ABCB1 or MDR1) are involved in IM removal, whereas human Ion transporter 1 (hOCT1) has a role in intramuscular (IM) absorption. Cytochrome P450 Cytochrome P450 3A4 and CYP3A5 are the main enzymes in cat the metabolism of IM. Several research have examined the genes that encode these proteins and how they relate to the pharmacokinetics and responsiveness to intramuscular (IM) administration, as previously described

Imatinib Pharmacokinetics

Oral administration of imatinib results in peak plasma concentrations at 2 hours after dosing. Its binding concentration to plasma proteins is around 95%, and its estimated distribution volume ranges from 170 to 430 L. Imatinib has a total clearance of It is mostly excreted by the liver (9–14 L/h) and has a half-life of 12–34 hours; the kidneys remove less than 15% of it. Plasma protein binding fluctuations and intrinsic hepatic clearance define steady-state total plasma concentrations of imatinib, which are affected by its low hepatic extraction rate (approximately 15 L/h). (metabolism and transport).

Since drug name: imatinib acts within cells, the efficiency of the drug may depend on factors such as the degree to which it reaches its target CML cells, which may vary. Yet, no actual evidence of a link between intracellular concentration and response in CML cells has been examined or shown in vivo at this time. Figure 1 provides a summary of the main factors influencing imatinib disposition, which are further examined in the following sections.

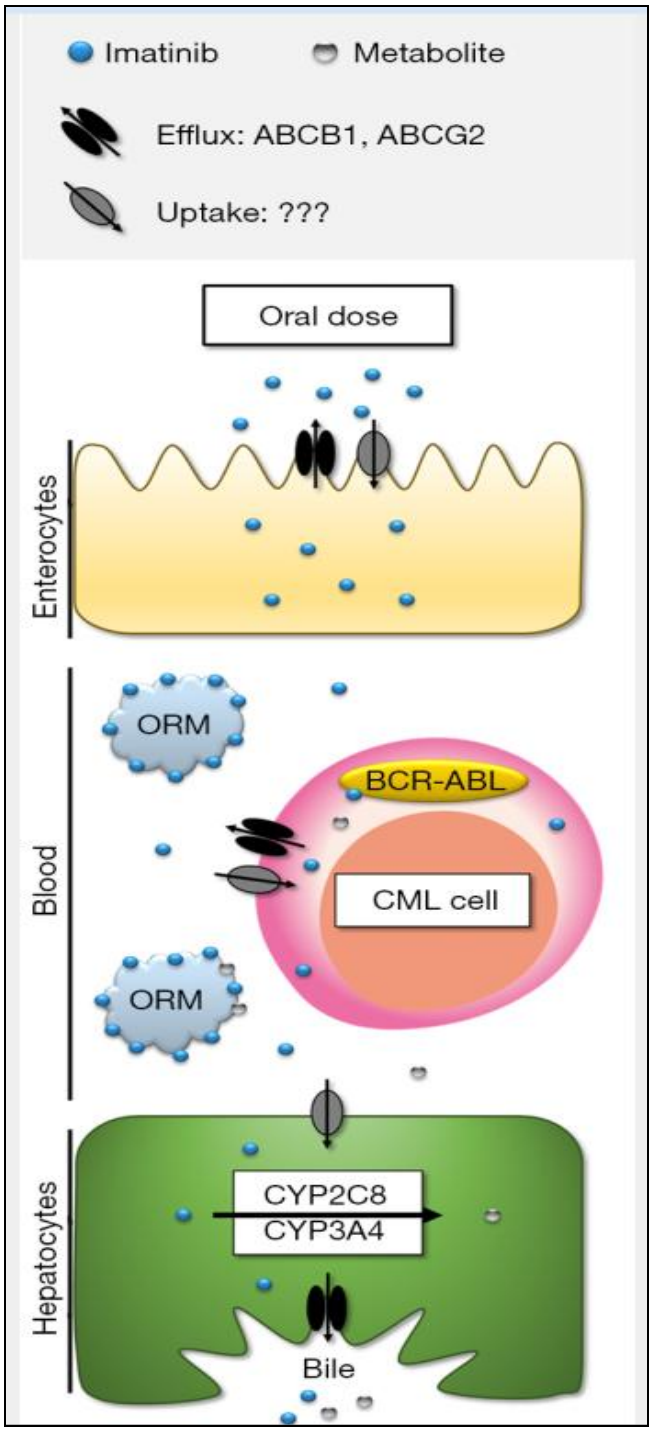

Fig 1: Essential factors influencing the disposition using imatinib for those with chronic myeloid leukemia. Chronic myeloid leukemia (CML) and orosomucoid/alpha-1-acid glycoprotein (ORM) are abbreviations for the same thing.

Plasma protein binding

The majority of imatinib (~95%) is linked to amphipathic glycoprotein (AAG) and other plasma proteins. The amount of unbound imatinib that may be cleared and distributed into CML cells is determined by the plasma AAG concentrations, which differ in CML patients by more than five times. As a result, the total plasma imatinib The gradient between concentration and response is complex, and total imatinib clearance varies greatly from one person to the next. is greatly impacted by varying plasma AAG concentrations (~10-20% of the coefficient of variation).

Metabolism

Hepatic N-demethylation converts imatinib to its primary the much less effective metabolite N-desmethyl imatinib (NDIM), whose IC50 is three to ten times greater. The total concentrations of NDIM in the plasma at steady state are around twenty percent of imatinib's. The majority of the excretion of imatinib and NDIM occurs in the liver, with little involvement from the kidneys. Since An abundance of diversity exists in plasma concentrations from patient to patient, the biotransformation of imatinib to NDIM is a crucial inactivating step from a therapeutic perspective.

Enzymes like CYP3A4, CYP2C8, and maybe CYP3A5 N-demethylate imatinib in vitro using recombinant enzymes; enzymes like There is little to no impact seen for CYP1A2, CYP2D6, CYP2C9, and CYP2C19. Research on healthy individuals using single doses of imatinib has shown that the enzyme CYP3A4 influences the drug's in vivo metabolism. These data, together with the relative abundance of hepatic CYP3A4 compared to CYP2C8, have long led to the belief that CYP3A4 is the primary or only enzyme responsible for the metabolism of imatinib in patients with chronic myeloid leukemia (CML).

Nevertheless, CYP3A4 inducers and inhibitors imatinib's steady-state pharmacokinetics are unaffected., and the heterogeneity in CYP3A activity indicators in patients with CML or GIST is unrelated. A possible explanation for the observed the current discovery contrasts the dose- and time-dependent mechanism-based suppression of CYP3A4 in prior in vitro studies by suggesting that imatinib N-demethylation in human liver microsomes is mostly mediated by CYP2C8, rather than CYP3A4. investigations with imatinib. Imatinib metabolism may be significantly impacted by CYP2C8 metabolism, according to recent findings., casting doubt on the long-established involvement of CYP3A4 in this process.

Transport

Drug transporters that control the uptake and efflux of imatinib might potentially impact imatinib disposal on many levels, as seen in Figure 1. Imatinib absorption may be aided, for instance, by uptake transporters found in enterocytes. At pH 6 and below, imatinib is mostly cationic; it contains acid dissociation constants (pKa) and is a quadrivalent base. of 1.52, 2.56, 3.73, and 8.07. One possible explanation for imatinib's high bioavailability is its active intestinal absorption mechanism. While efflux transporters may inhibit the absorption of imatinib, the fact that imatinib has a high bioavailability suggests that efflux transporters aren't really that important. Extensive in vitro research has focused on the causes to imatinib, both initially and later on; however, it is also possible that drug transporters contribute to the uptake and maintenance of imatinib in cancer cells that are intended to be treated. The distribution coefficient (logD) of imatinib is 0.8 at pH 7.4, and it is partly charged (~33% noncationic). Nevertheless, imatinib shows an active absorption mechanism as a result of its the peripheral blood mononuclear cells of patients had a high ratio of intracellular to plasma levels (~8). Last but not least, hepatocyte-expressed influx and efflux transporters may aid in the biotransformation and excretion of imatinib, which would increase its clearance.

Here is a summary of the expert opinions about imatinib

from a recent comprehensive evaluation of evidence addressing the influence of drug transporters on TKI disposal:

Efflux

The distribution of imatinib is drastically changed in mice that lack either ABCB1 or ABCG2, since these transporters bind to Protein G and the breast cancer resistance protein (BCRP) respectively.

Uptake

Despite SLC22A1's long-standing reputation as an important imatinib transporter, recent OCT1 has almost little involvement in the absorption of imatinib, according to in vitro and in vivo investigations. Likewise, SLC22A2-8, SLC47A1, SLCO1B1, and SLCO1B3 are not uptake transporters that have been shown to substantially affect the intracellular accumulation of imatinib. That is why we still don't know which transporter(s) are primarily responsible for imatinib absorption.

We agree with Neul and colleagues that better ways to measure imatinib transit would be to use assays that are more suitable, well-designed, controlled, and standardized. The pharmacogenetic investigations of transporters that were before thought to be unimportant to the disposition of imatinib may have wasted a lot of time and money, as will be shown below. There has been a lack of research into how factors like transporter variability (such as expression, inhibition, or heredity) affect the intracellular concentrations of imatinib in patient cells. This, combined with clinical demonstration of an intracellular concentration-response connection for imatinib, is essential for improving patient outcomes from the vast amounts of data conducted regarding pharmacogenetic investigations and transporter-mediated imatinib resistance mechanisms in vitro.

Pharmacogenomics: Driving Personalized Medicine

Age, sex, illness state, weight, socioeconomic position, and typical diagnostic measures like glucose and cholesterol levels are personal traits that direct effective disease prevention and therapy. We now have a better grasp of personalized medicine thanks to recent scientific and technical developments, such as genomics, which have greatly improved our capacity to optimize medications that are specific patients in certain categories or even on an individual basis. On page 85, it is stated: "personalized healthcare is an approach to care that utilizes personalized medicine tools to deliver patient-centered, predictive care within the context of coordinated service delivery." This clarifies the significance of tailored healthcare and aids in dispelling misconceptions. "Health care" refers to a more comprehensive set of services with the overarching goal of promoting optimal health, while "Personalized health care" and "personalized medicine" are words that may mean the same thing most of the time. Instead, then focusing on potential causes of illness, these programs encourage clients to build resilience. and need different methods philosophically.

Modern anti-cancer medication therapy has come a long way in the last few decades. Still, there is a wide range in pharmacological response and survival rates among patients given the same treatment plans. Consequently, standard approaches to deciding on a course of therapy considering just environmental factors like age and sex, as well as clinical and histopathological variables cannot adequately account for all patients. More and more focus is being placed on meticulously analyzing genetic profiles when cancer patients are being monitored, thanks to the rise of high-throughput genetic analysis methodologies and human genome sequencing technology. This is because it is now indisputable that a person's genetic makeup may impact how drugs work.

Genomic medicine is becoming a big part of customized care, and some people are even advocating for the idea of "precision medicine" that targets each patient specifically. Yet, there have been significant roadblocks to using genomics in clinical practice, mainly owing to the complicated interplay between genetic variables and symptoms. Nowadays, genomics covers a wide range of -omics, from proteomics to metabolomics and beyond, all of which provide biomarkers that may be used as therapeutic guidelines. When it comes to medication treatments, pharmacogenomics has become a major force in customized medicine, and many personalized medicines have entered clinical trials; yet, there are still many obstacles to be addressed. This review discusses the potential and constraints of pharmacogenomics in a broad sense.

An integral aspect of precision medicine, pharmacogenomics is finding more and more applications in clinical practice to enhance pharmacological treatment, especially about cancer. The fields of pharmacogenomics and pharmacogenetics refer to the same thing. While genomes g*et al*l the attention in the context of precision medicine, the word really encompasses the use of any clinical characteristic to tailor individual patients' medication regimens. Given that heredity sequencing technology have advanced and there is more evidence to suggest gene-drug connections, doctors may use genetic data to personalize treatment plans. Cancer, a disease caused by a mutation in DNA, is one of the most promising new fields for clinical pharmacogenomics research and development. Indeed, tumor profiling (genetic sequencing) has become the gold standard in several cancer centers and for some forms of cancer (e.g., lung, breast, melanoma, colorectal).

There are two genomes involved in cancer pharmacogenomics: the patient's and the tumors. All of these provide useful data for tailoring pharmaceutical treatments to each patient. Standard dosages of certain chemotherapeutic medicines may cause severe toxicity or therapeutic failure in particular patients, and this is because the patient's genome-inherited genetic variation-reveals information about the functioning of essential drug-metabolizing enzymes. Optimizing the selection and dosage of different supportive care drugs may also be possible with an understanding of genetic variances in the patient's genome. The tumor genome, which is a kind of acquired genetic variation, may help pinpoint the mutation(s) that are driving uncontrolled cell development. By targeting these mutations with the right medication, the tumor can be reduced in size. The best course of therapy may be dictated in part by genetic abnormalities found within the tumor genome, which may be associated with prognosis. Compared to conventional cytotoxic chemotherapy, which

targets both cancer and healthy tissue, targeted therapies-medications that aim at a particular genetic mutation in the tumor genome-may have fewer side effects. In order to confirm that a targeted treatment is suitable and may have a therapeutic effect, genetic testing must be conducted prior to administration.

Pharmacogenomic testing is still not widely available due to financial concerns and the reluctance of insurance companies to provide coverage for it unless it is absolutely necessary before prescribing a certain medicine. Having said that, more and more people are able to have testing done. Both proactive and reactive strategies are used in pharmacogenomic testing. When considering or beginning a medication therapy, reactive testing may help with drug selection or dosage for a particular indication, or it might explain why a treatment has failed or what side effects have been encountered. In most cases, a single gene is tested for in reactive testing. Preemptive testing, on the other hand, sometimes entails testing for a panel of genes beforehand; this kind of testing is not reliant on the patient's current or future prescription regimen.

The goal is to gather this data ahead of time so that it may be used just when required so that when it comes time to choose and administer medicine, care. When compared to testing individual genes at various intervals, preemptive pharmacogenomic testing for a panel of genes is much more cost-effective per gene. There may be a substantial return on investment for preventative testing throughout the course of a patient's lifetime because to the pharmacogenomic tests' everlasting clinical utility. To get the most of this ROI, you need to include the findings into your EHR with clinical decision support tools.

Conclusion

In conclusion, the integration of personalized medicine and pharmacogenomics into healthcare represents a significant advancement in tailoring treatment to individual patients based on their unique genetic profiles and other personal characteristics. This approach enhances disease prevention and therapy by utilizing genomic data to optimize medication regimens, particularly in cancer treatment, where understanding both the patient's and tumor's genomes can lead to more effective and targeted therapies with fewer side effects. Despite the potential benefits, challenges such as financial barriers and insurance coverage remain obstacles to widespread adoption of pharmacogenomic testing. However, proactive strategies like preemptive testing for gene panels can offer cost-effective solutions and improve patient outcomes over time. As the field continues to evolve, the incorporation of pharmacogenomic data into electronic health records and clinical decision support systems will be crucial for maximizing the benefits of personalized healthcare.

References

1. Barratt DT, Somogyi AA. Role of pharmacogenetics in personalised imatinib dosing. Translational Cancer Research. 2017;6(Suppl 10):S1541–S1557. doi:10.21037/tcr.2017.09.08.
2. Ankathil R, Husin A, Dzarr AA, Baba AA. Pharmacogenetics and the treatment of chronic myeloid leukemia: how relevant clinically? An update. Pharmacogenomics. 2018;19. doi:10.2217/pgs-2017-0193.
3. Singh DB. The impact of pharmacogenomics in personalized medicine. In: Pharmacogenomics. 2019. doi:10.1007/10_2019_110.
4. Nimra M, Robab S, Rasool M. Pharmacogenomics of leukemia: unlocking personalized treatment strategies. Precision Medicine Communications. 2023;3:151–160. doi:10.55627/pmc.003.02.0388.
5. Zaker E, Nouri N, Sorkhizadeh S, Ghasemirad H, Hajijafari A, Zare F. The importance of personalized medicine in chronic myeloid leukemia management: a narrative review. Egyptian Journal of Medical Human Genetics. 2023;24. doi:10.1186/s43042-023-00411-3.
6. He S, Shao Q, Zhao J, Bian J, Zhao Y, Hao X, et al. Population pharmacokinetics and pharmacogenetics analyses of imatinib in Chinese patients with chronic myeloid leukemia in a real-world situation. Cancer Chemotherapy and Pharmacology. 2023;92. doi:10.1007/s00280-023-04581-0.
7. Polillo M, Galimberti S, Baratè C, Petrini M, Danesi R, Di Paolo A. Pharmacogenetics of BCR/ABL inhibitors in chronic myeloid leukemia. International Journal of Molecular Sciences. 2015;16:22811–22829. doi:10.3390/ijms160922811.
8. Kumbhar S, More M, Jadhav P. A review: pharmacogenomics and personalized medicine. International Journal for Research in Applied Science and Engineering Technology. 2023;11:483–491. doi:10.22214/ijraset.2023.57183.
9. Rasmussen A, Andersen C, Weimann A, Yang T, Tron C, Gandemer V, et al. Therapeutic drug monitoring of imatinib: how far are we in the leukemia setting? Expert Review of Clinical Pharmacology. 2024. doi:10.1080/17512433.2024.2312256.
10. Alarcón-Payer C, Suárez M, Roldán A, Puerta J, Morales A. Impact of genetic polymorphisms and biomarkers on the effectiveness and toxicity of treatment of chronic myeloid leukemia and acute myeloid leukemia. Journal of Personalized Medicine. 2022;12:1607. doi:10.3390/jpm12101607.
11. Khan A, Hakim Z, Waheed A, Abrar. Impact of CYP3A4 rs2242480 polymorphisms on imatinib HPLC-determined trough concentration and response in chronic myeloid leukaemia in Pakistani patients. F1000Research. 2024;13:310. doi:10.12688/f1000research.146356.1.
12. Kaehler M, Cascorbi I. Pharmacogenomics of impaired tyrosine kinase inhibitor response: lessons learned from chronic myelogenous leukemia. Frontiers in Pharmacology. 2021;12:696960. doi:10.3389/fphar.2021.696960.
13. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. New England Journal of Medicine. 2017;376:917–927. doi:10.1056/NEJMoa1609324.
14. Ravegnini G, Sammarini G, Angelini S, Hrelia P. Pharmacogenetics of tyrosine kinase inhibitors in gastrointestinal stromal tumor and chronic myeloid leukemia. Expert Opinion on Drug Metabolism and Toxicology. 2016;12.

doi:10.1080/17425255.2016.1184649.
15. Shriyan B, Mehta P, Patil A, Jadhav S, Kumar S, Puri A, et al. Role of ADME gene polymorphisms on imatinib disposition: results from a population pharmacokinetic study in chronic myeloid leukaemia. European Journal of Clinical Pharmacology. 2022;78:1–10. doi:10.1007/s00228-022-03345-8.