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Pharmacogenomics and Precision Dosing: A Modern Approach to Reducing Adverse Drug Reactions

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***Abstract*—The research of the genetic variation in the individual responses to drugs has become one of the pillars of personalised medicine and this field has been labelled as pharmacogenomics. Pharmacogenomics facilitates the clinical practitioner to individualize therapy by pinpointing any genomic variations that influence drug absorption, distribution, metabolism, and activity. It is the reason why a personalised approach is especially significant since adverse drug reactions (ADRs) are a significant clinical and public-health issue of concern on an international scale, as they cause significant morbidity, mortality, non-compliance, and increased healthcare expenses. A combination of pharmacogenomic understanding and precision dosing, which involves incorporation of genetic information in conjunction with clinical factors including age, comorbidities, organ functioning and concomitant treatment, provides a more precise approach to optimisation of drug choice and dose as well as minimising unnecessary toxicity. The paper focuses on the principles of pharmacogenomics, genetic predictors of drug reactions, and the most important gene-drug interactions that are linked to the risk of ADR. It also discusses the technological advances that allow the use of a specific dose, clinical case studies in real-life practice, the existing barriers to its implementation, and the worldwide policy that promotes the use of personalised therapeutics. In general, the integrative application of pharmacogenomics and precision dosing is a radical move towards safer, predictive and patient-intelligent pharmacotherapy.**

***Keywords*—Pharmacogenomics, precision dosing, adverse drug reactions, CYP450, gene–drug interactions, clinical genomics, therapeutic drug monitoring, personalized medicine, genetic biomarkers, drug metabolism.**

I. Introduction

The problem of Adverse drug reactions (ADRs) is one of the principal international issues that cause numerous adverse effects in terms of morbidity, mortality, delayed hospitalization, and excessive spending on healthcare [1]. The traditional approaches of prescribing are based, to a great extent, on the population-based dosing guidelines, as they suggest that every patient will react in the similar way to the standard doses of drugs. Nevertheless, in the clinical reality, the responses to them differ significantly because of age, organ functioning, comorbidities, polypharmacy, lifestyle, and, most importantly, genetic composition [2], [3]. Such genetic variations have an effect on the pharmacokinetic and pharmacodynamic processes of the drugs, their metabolism, transport, receptor binding, and the overall therapeutic effects.

The study of these gene-drug interactions is known as pharmacogenomics (PGx), and thus has become a relevant area of concern in contemporary healthcare. It allows the determination of genetic attributes that predispose to ADRs or therapeutic failure. Knowledge of the effects of particular genetic polymorphisms on drug behaviour allows clinicians to minimize the trial and error method of prescription that is often linked with prescribing. This specific knowledge is the basis of the enhancement of drug safety, especially of drugs having a narrow therapeutic index or having a genetic risk. The possibility of personalised therapy is further enhanced by the combination of both pharmacogenomics and precision dosing. Precision dosing combines both genetic data and clinical data (age, renal and hepatic working, disease severity, and drugs used in combination with each other) to work out the minimum dose that is correct and safe in each particular case. This is a combined method that does not only reduce the number of ADRs but it also improves the efficiency of the treatment, maximizes the drug exposure and helps in achieving better predictability and patient-centred pharmacotherapy. With the global healthcare systems shifting to the paradigm of personalised medicine, pharmacogenomics and precision dosing have emerged as the key to enhancing clinical outcomes and making therapeutic decisions safer.

II. Pharmacogenomics: Concepts and Foundations

A. Definition of Pharmacogenomics

Pharmacogenomics can be referred to as the examination of the role of genomic differences in the responsiveness of an individual to drugs and combines concepts of pharmacology, molecular genetics, and clinical practice [4], [5]. Although conventional pharmacogenetics usually only tests the relationship between single genes and drugs (see in Figure 1), pharmacogenomics broadens this view in terms of testing the relationship between multiple genes and the genome-wide interactions all at once. This wider attention enables better predictions of effectiveness of drugs, toxicity and optimum dosage in genetically differentiated groups. With the recent developments in the genomic sequencing technology, personalised medicine has placed more emphasis on the field of pharmacogenomics, which has allowed clinicians to

personalise therapy according to the individual genetic profile of a patient.

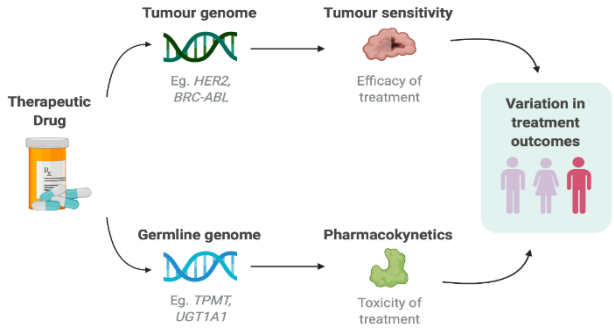

Fig. 1. Aspects of cancer pharmacogenomics

B. *Variability of Drug Response and Genetic Influence*

Inter-individual difference in the response to drugs is affected by many things, and genetic polymorphism is one of them that has a significant effect. Genetic differences in pharmacokinetic (PK) pathways, including processes that regulate drug absorption, distribution, metabolism, and elimination, may also change the levels of drugs in circulation, with the consequence of either therapeutic failure or toxicity. In the same way, PD differences affect the pharmacodynamic drug-target interactions, receptor sensitivity, and downstream signalling pathways. Research also shows that more than 90 percent of individuals have at least one pharmacogenomic variant to act on [6], [7]. As an illustration, those with CYP2D6 gene duplications can convert codeine to morphine quickly, which can cause toxicity but carriers of CYP2C19 loss-of-function alleles can fail to activate clopidogrel efficiently to prevent antiplatelet therapy.

C. *Role of ADRs in Global Health*

Adverse drug reactions (ADRs) represent 5-10 percent of hospitalization worldwide, and it is one of the leading causes of morbidity and death in patients. The clinical manifestations could be mild in gastrointestinal disturbances and severe like Stevens Johnson syndrome (SJS). The cost of the economy is enormous with billions of dollars in preventable care and readmission [8]. Numerous ADRs develop due to genetic changes in the metabolism or immune response of drugs. Pharmacogenomics can be a useful solution to these risks as it allows customising drug choice and dose and enhances safety and therapeutic results.

D. *Impact of Pharmacogenomics in Precision Medicine*

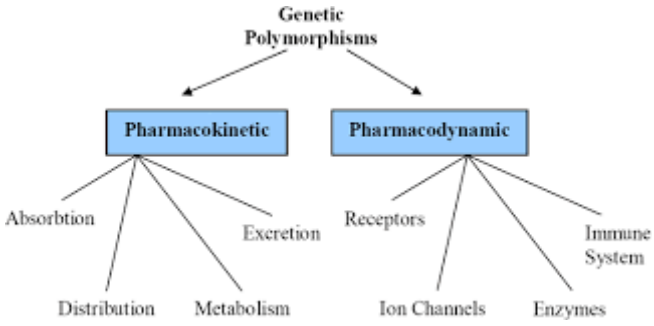

Fig. 2. Types of Genetic Polymorphisms

Pharmacogenomics is a key to precision medicine as it allows the drug treatment to be customized to the genetic pattern of a person as opposed to general population tendencies. It improves the choice of drugs, the precision of dosing, and the safety of treatment in general by determining genetic variants of metabolism, transport, targets, and immune pathways [4]. Genotype-guided prescribing of drugs like clopidogrel, warfarin, abacavir and thiopurines has led to a large proportion of adverse drug reactions and improved therapeutic response. Pharmacogenomics is also the least invasive due to minimum trial and error prescription, drug response predictability, and enhanced efficiency in healthcare (see in Figure 2). With the introduction of genomic technologies into clinical systems, pharmacogenomics enhances personalised, safer, and more effective pharmacotherapy in the contemporary healthcare.

III. Old-fashioned Prescribing vs Accurate-Based Processes

A. *Shortcomings of Traditional Doses*

The traditional methods of prescribing are founded on population averages determined using clinical trials to a great extent. These rules can be helpful as initial dosing, but they do not take into account the significant inter-individual differences and assume that the majority of patients will react equally to the standard drugs [9]. Such a homogenous strategy is not very effective to explain genetic polymorphisms that determine drug metabolism, transportation and receptor interactions. This means that the traditional dosing process usually fails to forecast treatment results in patients that either react quickly or slowly to drugs.

Other limitations are also that there are problems in determining the extreme responders and non-responders, higher chances of concentration-related toxicity and also it is not applicable in vulnerable populations such as paediatric, geriatric and multi-morbid patients. Such groups will usually have some distorted pharmacokinetics that cannot be sufficiently treated using standardised dosing [10]. This is especially problematic when the drugs with small therapeutic indices (warfarin, tacrolimus, phenytoin, and aminoglycosides) are involved, and minor changes in the dosing regimen can cause severe adverse drug reactions (ADRs) or a lack of therapeutic effect. Therefore, traditional prescribing is still beneficial, but it is not as exact as it should be to guarantee maximum safety and effectiveness to every patient.

B. *Advantages of Pharmacogenomic-Guided Prescribing*

Pharmacogenomic prescribing is more sophisticated and personalised, as it introduces the element of genetic data in the decision-making process in therapeutic procedures. The approach enables stratification of risks depending on the metabolic profile of a patient, which minimizes the risk of developing ADRs and enhances the safety of drugs [11]. It also improves therapeutic efficacy due to proper exposure of the drug used and allows the choice of alternative medication in those individuals who are genetically prone to poor response. Pharmacogenomic guidance enhances patient satisfaction and clinical efficiency by diminishing trial-and-error medicine prescriptions. It has been indicated that these customized strategies enhance compliance and result in overall enhanced treatment outcomes [12]. Finally, pharmacogenomic-based prescribing facilitates the transition to individualised medicine, which is a safe, most effective, and more economical model of care.

IV. Drug Response Genetic Determinants

The genetic determinants play an important role in the behavior of individuals in response to medications, which influences the outcome of the therapy and predisposition to adverse drug reactions (ADRs). Genetic variations in drug-metabolising enzyme, transporter, drug target, and immunological response molecule gene encoding can be important in both pharmacokinetic (PK) and pharmacodynamic (PD) routes [11]. Knowledge of these genetic factors makes clinicians able to anticipate the variability of individuality in terms of drug exposure, sensitivity, and toxicity, which constitute a major basis of personalised medicine. Table I shows the gene-drug interactions.

TABLE I. Clinically Relevant Gene–Drug Interactions

Gene / Variant	Affected Drug(s)	Effect of Variant	Clinical Implication
CYP2D6 PM/UM	Codeine, Tramadol	PM: Poor activation; UM: Excess morphine formation	Avoid codeine in PM/UM; use alternatives
**CYP2C19 2/3	Clopidogrel	Reduced drug activation	Switch to prasugrel/ticagrelor
**CYP2C9 2/3	Warfarin	Reduced metabolism	Lower initial dose to prevent bleeding
*SLCO1B1 5	Simvastatin	Reduced hepatic uptake → ↑ toxicity	Use lower dose or alternate statin
HLA-B*57:01	Abacavir	High risk of hypersensitivity	Contraindicated; test before use
HLA-B*15:02	Carbamazepine	Risk of Stevens-Johnson Syndrome	Avoid drug in carriers

A. Drug-Metabolising Enzymes

The biotransformation of most drugs needs drug-metabolising enzymes, most notably those of the cytochrome P450 (CYP450) family. The genetic polymorphisms in these enzymes tend to cause changes in the enzyme activity that generate clinically significant drug metabolism differences. CYP enzymes convert drugs into active or inactive metabolites, and genetic variants can significantly increase or decrease enzyme activity, affecting drug concentration and therapeutic action.

1) CYP2D6

CYP2D6, known to metabolise about a quarter of all therapeutics, antidepressants, opioids, antipsychotics, and 80% of 80% of 90% of 20% of 100% of 25% of 30% of 40% of 50% of 60% of 70% of 80% of 90% of 100% of 110percent of 120% of 130% of 1 Allelic variants have been defined and there are more than 100, leading to a range of metaboliser phenotypes, including poor (PM), intermediate (IM), extensive (EM), and ultra-rapid (UM) metabolisers [13]. PMs demonstrate a highly decreased activity of enzymes, which rises plasma levels of medications and risk of toxicity, whereas UMs can eliminate drugs in a short period of time, resulting in a decrease in therapeutic effect and possible treatment failure. In the case of codeine which is classified as an opioid drug, UMs can overchange codeine to morphine leading to severe toxicity. CYP2D6 breaks down numerous antidepressants, antipsychotics, beta-blockers and opioids. The variants of its genes produce either poor or ultra-rapid metabolisers resulting in incomplete drug effect or toxicity. As an example, CYP2D6 enzyme conveys the transformation of codeine to morphine, which affects the safety and efficacy. Genotyping assists clinicians not to prescribe codeine to at-risk patients but to use safer options.

2) CYP2C19

Some of the key drug classes that cyprosate is metabolized in are proton pump inhibitors, antiplatelet therapy, and some antidepressants. The alleles of loss-of-function (*2 and *3) reduce the activity of enzymes, restricting the activation or the elimination of drugs [14]. In the case of clopidogrel, which is a prodrug that needs the activation of CYP2C19, platelets should be inhibited by carriers of such variants, which can lead to insufficient cardiovascular event prevention. On the other hand, the fast metabolisers can clear up some drugs too fast and reduce its effect. Clopidogrel is a prodrug requiring CYP2C19 activation. Patients with loss-of-function alleles cannot adequately activate the drug, leading to poor platelet inhibition and increased cardiovascular risk. Clinically, CYP2C19 testing allows prescribers to switch to prasugrel or ticagrelor for better outcomes.

3) CYP2C9

CYP2C9 is important in metabolism of warfarin, NSAIDs and various antidiabetic drugs. CYP2C92 and CYP2C93 variants have a significant effect of reducing the functionality of the enzyme [6]. Regarding the warfarin treatment, reduced metabolism increases the risk of bleeding complications in patients unless the dosage is adjusted. Reduced warfarin metabolism causes higher bleeding risk. Genotype-guided dosing improves safety by preventing over-anticoagulation.

B. Drug Transporters

Drug transporters control the drug entry and exit of cells affecting absorption, distribution and excretion [14]. Transporter gene genetic polymorphisms have the potential to significantly change the disposition of drugs.

1) SLCO1B1

SLCO1B1 is the gene that produces the hepatic transporter OATP1B1 that facilitates the absorption of statins in the blood to the liver cells. SLCO1B1*5 variant is associated with lower efficiency of the transporter leading to higher systemic statin levels and the risk of dose-related myopathy [15]. This variant should be identified as an important consideration in statin therapy, especially simvastatin. Patients with SLCO1B1*5 benefit from lower simvastatin doses or switching to pravastatin to reduce muscle toxicity.

2) ABCB1

ABCB1 is a gene, which encodes efflux transporter P-glycoprotein, which is expressed in the intestine, liver, kidney, and blood-brain barrier. Allotypes may affect the tissue drug penetration and systemic exposure of the drugs used such as digoxin, chemotherapeutics, and anti-epileptics [16]. The modification of P-glycoproteins activity can expose a drug to therapeutic failure or surprise toxicity based on the drug PK profile. Altered transporter activity can cause insufficient drug penetration or toxicity. Genotype knowledge helps adjust doses or choose safer alternatives.

C. Drug Targets and Receptors

Polymorphisms in drug targets and receptors may modify drug binding affinity, downstream signalling and clinical response.

1) VKORC1

VKORC1 codes vitamin K epoxide reductase complex, which is the pharmacological drug warfarin targets. This is a

-1639G to A polymorphism that causes warfarin hypersensitivity, with little maintenance anticoagulation being necessary to prevent bleeding complications [17]. Combining VKORC1 and CYP2C9 genotyping provides the most accurate warfarin dosing predictions.

2) ADRB1

ADRB1 gene is a β-adrenergic receptor, an antagonist of which is β-blockers in hypertension and heart failure. Genetic variations may affect the sensitivity of receptors whereby certain forms of genotype may show an increased or decreased therapeutic response [18]. Such variations may be used to direct the choice of drugs and dose optimization. Genotype-guided therapy helps clinicians choose the most responsive beta-blocker and dose.

D. Severe ADRs and Immunogenetics.

Human leukocyte antigen severe, immune-mediated ADRs have been strongly linked to genetic variations in its complex.

*1) HLA-B*57:01*

HLA-B57: 01 is a significant risk allele to abacavir hypersensitivity syndrome. Testing this allele is currently a norm across the globe and it has led to almost zero cases of this potentially deadly response [19].

*2) HLA-B*15:02*

Carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis are linked to HLA-B15:02 in East Asians. Before taking carbamazepine in people at risk, it is advisable to perform genetic testing to avoid severe cutaneous reactions. HLA testing is now a key preventive tool for safe prescribing in high-risk populations.

V. Precision Dosing Clinical Practice

Precision dosing has received a necessary upgrade in personalised medicine enabling clinicians to maximize drug therapy using a combination of pharmacokinetic, pharmacodynamic, and pharmacogenomic data [20]. The precision dosing strategy seeks to attain the optimal treatment drug concentrations that can be as effective as possible with minimal risk of adverse drug reactions (ADRs), taking into consideration the inter-individual variability. Several tools and strategies have been developed to facilitate this approach in clinical practice.

A. Therapeutic Drug Monitoring (TDM)

TDM is the act of measuring levels of drugs in plasma and using them to make alterations in dosage and to guarantee that therapeutic levels are attained. It is especially useful in case of medications with narrow therapeutic indices, which include vancomycin, tacrolimus, phenytoin, and lithium because minor changes in dosage may result in toxicity or ineffective treatment [21]. The combination of pharmacogenomic data with TDM allows the accuracy of doses to increase because genetic variants can considerably affect the effects of drugs on clearance and metabolism.

B. Bayesian Modelling and Dosing Algorithms

DoseMe and InsightRx are examples of Bayesian dosing systems that use the population pharmacokinetic models and single patient clinical and laboratory data to predict individualised dosing needs [22]. Genetic information may be included in these models, which leads to even more accurate predictions of doses, which enables clinicians to customize treatment to individual genotype and real-time patient data.

C. Integration with Electronic Health Records

The implementation of pharmacogenomic data into electronic health records (EHRs) will allow automatic notifications in the process of prescription-related activities, which will alert clinicians about the significant interaction between genes and drugs [23]. Such real-time alerts ensure safer decision making, avoid improper choices of medication, and adverse drug reactions because by identifying the genetic profile of each patient, treatment is personalized.

D. Clinical Decision Support Tools

Clinical decision support systems, such as CPIC-based calculators, gene-drug interaction dashboards, and automated risk notification systems, are systems that translate the outcomes of genetic tests into easy-to-understand and act-on recommendations about prescribing. These tools can make the complex pharmacogenomic data simplified, thereby making precision dosing more accurate and reliable, selecting safer drugs, and increasing confidence of clinicians as they incorporate genomics into the regular medical decisions they make.

VI. Cases of Pharmacogenomics

Pharmacogenomics is offering obvious clinical advantages in a number of therapeutic issues especially those drugs with small therapeutic indices or whose activation pathways are influenced by genotype. The case studies presented below indicate the well-known examples of the interaction between genes and drugs in which pharmacogenomic testing significantly enhanced the safety and effectiveness of the treatment.

A. Warfarin (CYP2C9/VKORC1)

There is a high inter-individual variation in the administration of warfarin therapy related to genetic variations in CYP2C9-mediated metabolism, and VKORC1-mediated drug sensitivity. Patients with reduced-function CYP2C9 alleles or the VKORC1 -1639G A phenotype typically have considerably smaller dosage requirements [16]. The genotype-guided dosing has been reported to cut short the time to get to therapeutic INR ranges and considerably reduce complications associated with bleeding.

B. Clopidogrel (CYP2C19)

Clopidogrel is a prodrug that has CYP2C19 activation. Alterations in its conversion to the active metabolite are caused by loss-of-function variants, resulting in insufficient platelet inhibition (2,3). Guidelines by CPIC suggest alternative antiplatelet therapies like prasugrel or ticagrelor to these patients as a measure of ensuring such a major cardiovascular event does not occur [11].

*C. Abacavir (HLA-B*57:01)*

One of the most successful pharmacogenomic interventions in clinical practice has been screening of HLA-B,57:01 prior to the commencement of abacavir treatment, which has almost completely eradicated the condition of hypersensitivity reactions.

D. Codeine/Tramadol (CYP2D6)

Ultra-rapid metabolisers (CYP2D6) change codeine and tramadol to active metabolites at undue levels, which cause toxicity especially in children. On the other hand, low

metabolisers have an insignificant analgesic effect [12]. Regulatory authorities recommend against the use of the drugs in the two phenotypes.

E. Thiopurines (TPMT/NUDT15)

TPMT or NUDT15 deficiency has a strong predisposition to thiopurine myelosuppression. Oncology and gastroenterology now use genotype-guided dose reductions, which enhance the safety and outcomes of the treatment [19].

VII. Issues and Adoption Barriers

Although pharmacogenomics has been shown to have the advantages, there are some obstacles that still impede its use in clinical practice. These issues cut across economic, educational, regulatory, scientific and ethical sectors, generating inequalities in access and implementation of healthcare systems.

A. High Cost of Testing

Genetic testing is a costly procedure although it has been made cheaper with time in most low-resource contexts. Insufficient insurance coverage also reduces access among the patients, hindering integration in the clinic.

B. Knowledge Gaps

A high number of clinicians are not well trained in the area of genomics and pharmacogenomic test results interpretation. These knowledge gaps should be addressed by educating and enhancing their professional skills [21].

C. Regulatory and Reimbursement Barriers

Inequitable legislation and inadequate policies on reimbursements pose ambiguity and demotivate health establishments to adopt pharmacogenomic services.

D. Database Limitations

Individuals of European descent are overrepresented in global pharmacogenomic databases, which lowers the efficacy of predicting individuals who are underrepresented, and restricts the ability to use them fairly [16].

E. Privacy and Ethical Issues

Genetic data are harmful to informed consent, data security, and abuses or discrimination. High privacy standards are crucial to ensure the integrity of the population.

VIII. Global Practices and Policy Guidelines

The inclusion of pharmacogenomics in healthcare has been facilitated by a number of guideline bodies and policy initiatives designed to standardise practice, enhance safety and equitable access.

A. CPIC and DPWG

Evidence-based, peer-reviewed, gene-drug recommendations are offered by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) [14]. The resources assist clinicians to use pharmacogenomic knowledge to optimize dose and enhance treatment outcomes.

B. FDA and EMA Biomarkers

Pharmacogenomic biomarkers are included in the drug labels by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and provide the prescribers with clear information on the genetic risks and dose modifications necessary.

C. National Genomic Initiatives

Large-scale, population-specific genomic projects are being created in major national programmes, including the All of Us Research Program in the USA, 1+ Million Genomes Initiative in the EU, GenomeIndia Project in India, and the Emirati Genome Programme in the UAE, which can be used to support personalised medicine [11].

D. WHO Strategy

The World Health Organization supports the idea of genomic equity in the world by means of the capacity-building, standardisation, and ethical introduction of genomic medicine [4].

IX. Discussion

Pharmacogenomics-based integration with precision dosing is a notable step forward in personalised medicine, which can be a proactive strategy of minimising adverse drug reactions to enhance therapeutic outcomes. The numerous examples of the gene-drug interactions prove that genetic and clinical data combined result in improved dosing, enhanced effect, and reduced treatment complications [8]. Nevertheless, even with high scientific evidence, widespread implementation is still inconsistent with the barriers of cost, lack of training of clinicians, and inconsistencies in regulatory systems. These gaps are being bridged through national genomic programs and new clinical practice guidelines, but fair implementation would need continued investment in education, data infrastructure and policy formulation. With the further evolution of genomic technologies and their increased accessibility, pharmacogenomic-directed precision dosing becomes even more likely to assume a more central role in the regular clinical practice.

X. Recommendations

A. For Policymakers

The policy-makers need to increase their national genomic testing programmes, compensate insurance reimbursement of pharmacogenomic services, and have clear regulatory and ethical guidelines.

B. For Healthcare Systems

Genomic data must be incorporated into electronic health records, and multidisciplinary teams of precision medicine must be established, which presupposes continuous training of the personnel.

C. Clinicians/Pharmacists

Clinicians are expected to use CPIC and DPWG guidelines, integrate genetic and clinical data, and teach patients the benefits of personalised therapy.

D. Researchers and Developers

The researchers need to expand the genomic research on different populations, improve pharmacogenomic databases, and develop decision-support tools that are easy to use.

XI. Conclusion

Precision dosing and pharmacogenomics is an emerging evidence-based therapy that reduce adverse drug reactions and enhance treatment results in a wide range of patients. Combining genetic data with clinical variables including organ functions, comorbidities, and overlapping medications, these approaches will provide a more efficient approach to

traditional population-based prescribing that is safer. Precision dosing can be used to increase the accuracy of the treatment through ideal drug exposure, whereas pharmacogenomics can be used to identify the people who are more likely to get toxicity or suffer a treatment failure. Despite the difficulties that still exist (e.g., testing expenses, inadequate training of clinicians and inconsistent regulations), improvements in genomic technologies and increasing national programs are causing clinical adoption to gain traction. With the growing trend toward personalised medicine in healthcare systems, there is a likelihood that the conception of the combined application of pharmacogenomics and precision dosing will be at the forefront of everyday clinical practice. In the end, such strategies will allow providing more predictable, patient-centred, and tailored pharmacotherapy, which will serve to make healthcare delivery safer and provide benefits in terms of long-term changes in treatment efficacy.

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