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1 Review

A Comprehensive Review: Pharmacogenomics and Personalized Medicine Customizing Drug Therapy Based on Individual Genetics Profiles

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Abstract Numerous factors, such as genetics, environmental factors, and illness determinants, might contribute to an unpleasant pharmaceutical response. In an effort to increase efficacy and safety, as well as to gain a better understanding of drug disposition and clinical consequences, researchers in the two quickly emerging fields of pharmacogenetics (which focuses on single genes) and pharmacogenomics (which focuses on many genes) have studied the genetic personalization of drug response. This is due to the fact that a large number of pharmacological responses seem to be genetically based, and the relationship between medication response and genotype may be important for diagnosis. We now have a better understanding of the genetic basis of individual medication responses because to research on pharmaceuticals and genes. Pharmacogenomics aims to improve patient outcomes by developing personalized medicine by using the diversity of the human genome and how it affects medication response. Translational in nature, pharmacogenomics research encompasses everything from the discovery of genotype-phenotype associations to clinical investigations that might show therapeutic relevance. Though the conversion of pharmacogenomics research findings into clinical practice has been sluggish, advances in the field offer considerable potential for future therapeutic applications in specific people.

Keywords Pharmacogenomics, Genes, Pharmacogenetics, Medicine, Pharmacological

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1. Introduction

Precision medicine's ultimate goal is to perfectly match each treatment intervention to the patient's molecular profile. Over the last two decades, cutting-edge sequencing technology have spurred research into human genetics, resulting in a better knowledge of the link between genetic variation and human health. Genetics research has been widely employed in precision medicine, with one emerging application being pharmacogenomics-informed pharmacotherapy, which tailors drug selection and dose to the patient's genetic characteristics. To date, pharmacogenomic variation has a well-established function in pharmacological efficacy and safety, allowing worldwide scientific consortia to develop treatment guidelines for the clinical use of pharmacogenomics[1]. Various genotyping approaches, including PCR and microarray-based assays, can be used to search for known pharmacogenomic markers in well-documented genes[2]. Only in rare cases can a genetic or genomic profile determine therapy. Other factors such as age, gender, body mass, and potential drug-drug interactions must also be considered. Physicians must make an informed clinical decision about treatment[3]. As pharmacogenomics advances from research labs to clinical settings, its impact can be felt in a wide range of medical fields. Pharmacogenomics-guided medicine selection is highly useful in oncology, which is distinguished by the wide range of malignancies and therapy responses. Genetic testing influences the selection of personalized drugs, increasing the likelihood of treatment effectiveness while reducing unnecessary side effects. Psychiatry is evolving as genetic indicators drive the selection of psychotropic medicines, hence enhancing patient wellbeing and treatment adherence [4]. The ideal genetic profiles will include gene variants that identify individual disease susceptibility and risk of progression to more severe disease, predict which pharmacologic therapies will provide the greatest therapeutic benefit, or predict whether a therapy will cause an adverse reaction and should be avoided in a given individual [5]. Despite the abundance of genetic data, there is still much to learn about gene function and its impact on disease phenotypes and treatment responses. Pharmacogenomics helps bridge the gap between basic research and clinical applications, leading to more cost-effective and efficient medication development [6]. Variations in drug metabolism enzymes and transporters can affect the pharmacokinetics and pharmacodynamics of medicines and their metabolites at the target site, resulting in different pharmacological reactions and interactions. Also environmental and microbiomes interactions Fig 1[7].

2. Pharmacogenomics in Clinical Practice

Healthcare practitioners have challenges in interpreting genetic data, implementing standard recommendations, and incorporating pharmacogenomic information into electronic health records. Despite this Pharmacogenomic

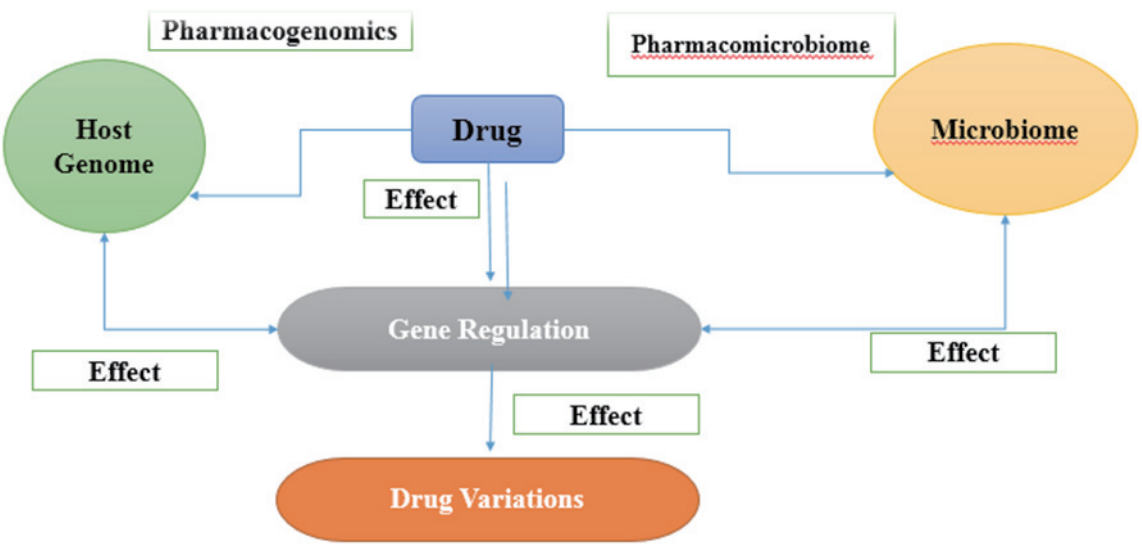

Figure 1. Microbial Interaction

testing is becoming more common to inform drug dosing decisions, despite its limitations[8]. Pharmacogenomics (PGx) examines how genetic variation influences drug response.(1-4) The consequences of genetic diversity might range from catastrophic, potentially fatal adverse medication reactions to a lack of therapeutic efficacy. Implementing pharmacogenomics at the point-of-care can help avoid adverse drug reactions, maximize efficacy, reduce drug-drug interactions, and select drugs based on patients' genetic profiles[9]. Pharmacogenomics implementation in clinical practice faces challenges like as testing availability, evidence-based prescribing recommendations, and EHR integration. Several studies show that doctors are unsure about how to handle pharmacogenomics information for patients and its impact on their clinical practices[10-14]. All of these findings have sparked renewed interest in pharmacogenomics, and several drug regulatory agencies, including the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), regard genetic factors that cause variability in drug response as an essential part of the drug development and approval process. Furthermore, it has been determined that correlations between genetic variations and clinical effects should be systematically provided in the package leaflet of all pharmaceuticals for whom such information is available. In the United States, it can be found in over 100 commercially accessible medications [15]. Finally, numerous pharmacogenomics consortia have been formed, notably the Clinical Pharmacogenetics Implementation Consortium (CPIC) [16-19].

3. Difficulties in Translating Pharmacogenomic Data into Clinical Practice

The identification of a biomarker is merely the first step in the long and arduous process of translating it into clinical practice. So far, the implementation of pharmacogenomic discoveries in clinical practice has been surprisingly unsatisfactory. In fact, many genetic biomarkers have not progressed far past detection. This lack of progress may stem, in part, from the failure to partially or completely duplicate research identifying genetic biomarker connections, which is not unusual in genetic research[20]. Environmental factors can also make it difficult to reproduce pharmacogenomic study results. It is predicted that only 10% to 15% of genetic indicators have a direct influence on treatment response. Instead, drug response phenotypes are frequently controlled by a complex interplay of environmental, genetic, and gene-environment factors. For example, it is known that tumor-associated inflammatory responses might inhibit CYP3A-mediated drug metabolism, contributing to the variability and toxicity of docetaxel (Taxotere, Sanofi-aventis; Docefrez, Sun) in cancer patients. Furthermore, drug interactions can affect drug response and frequently explain why a phenotype does not precisely match a genotype for drug metabolism[21-24]. This article discusses the difficulty of translating PGx to clinical practice. Figure 1 highlights six issues related to sequential steps of the translation process.Clinical practice examples illustrate each identified difficulty. Figure1 shows a number of "players" involved in the problems, including the biotechnology and analytical industries, pharmaceutical industry, research institutions, funding agencies, regulatory agencies, physicians, and patients. These people play key roles in designing and delivering clinical PGx applications, both individually and together [25-26].

4. Clinically Relevant Somatic Mutations

The cancer genome undergoes several rearrangements and may contain clinically significant genetic variants not observed in the germline. Somatic mutations acquired before or after treatment can impact medication effectiveness and toxicity. Gefitinib (Iressa) and erlotinib (Tarceva) inhibit the EGFR's tyrosine kinase domain. Approximately 10% of NSCLC patients who have failed traditional therapy have a related EGFR mutations may contribute to NSCLC resistance to gefitinib or erlotinib[27-28]. Recent improvements in NGS have substantially increased the viability of routine genetic testing of solid tumors, which was previously limited by sequential single-gene testing on small patient samples. NGS allows for simultaneous profiling of several genes from the same sample, minimizing patient wait time while improving the amount of information obtained from the test[29-30]. Molecular profiling in cancer seeks to find tumor DNA variants that can provide diagnostic, prognostic, or treatment-related information to help guide patient care. For example, evaluating lung cancer variations in EGFR exons 18-21 is recommended[31] to identify individuals with sensitivity or emerging resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Testing for RAS mutations is advised to improve patient care in colorectal cancer[32, 33]. The testing guidelines also

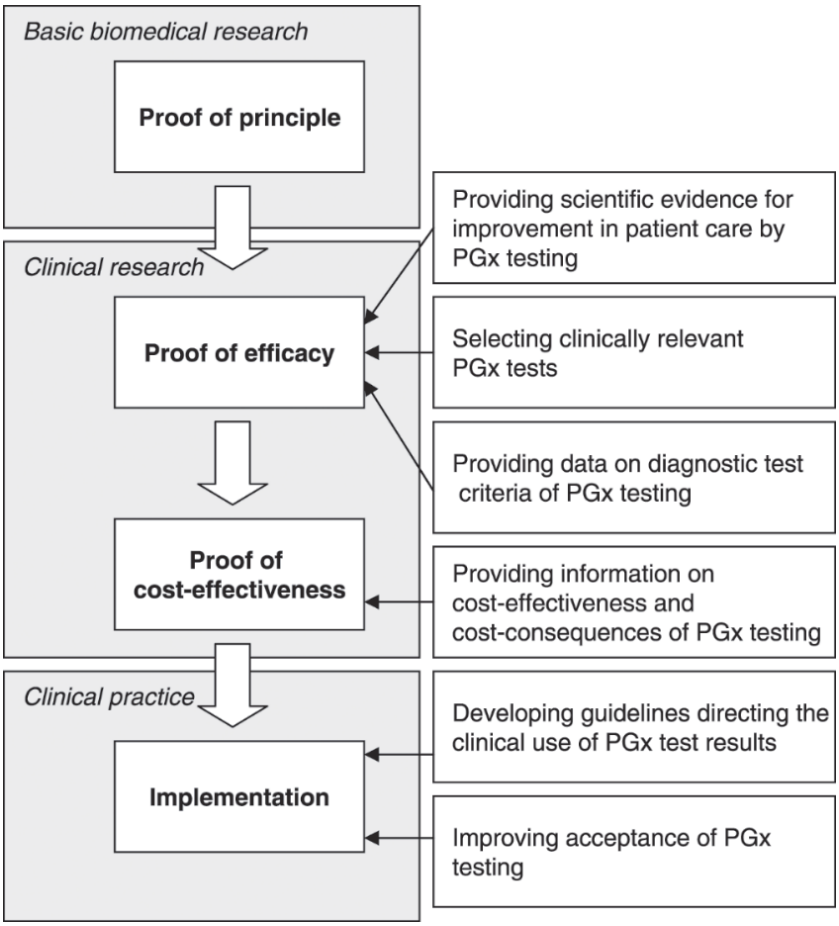

Figure 2. Consecutive Phases and Associated Challenges on the Road to Clinical Implementation of Pharmacogenomics.

advocate profiling melanoma patients for BRAF V600 variants[34] to identify people who benefit from BRAF TKIs, such as vemurafenib or dabrafenib[35]. Our assessment methodology (Figure 3) consists of the following points. First, sequencing data quality is examined, including coverage depth at variant site, in normal blood and formaldehyde fixed-paraffin embedded (FFPE) tumor tissues to confirm that somatic variant data meets minimum quality criteria [36,37] variations at or near quality and allele frequency thresholds are carefully explored, validated using an orthogonal method, and only interpreted and reported if verification is successful. The second step is to determine variation frequency in normal germ-line population datasets (the 1000 Genomes Project and the Exome Sequencing Project)[38]. Any mutation with a frequency in either database of >1% is considered benign and eliminated from further study. matic Mutations in Cancer (COSMIC)[39] and The Cancer Genome Atlas (TCGA) through the cBio Cancer Genomics Portal. The Cancer Genome Atlas (TCGA) through the cBio Cancer Genomics Portal[40]. If a variant is discovered in a gene for which locus-specific databases with somatic variant information exist, those databases are also searched. The International Agency for Research on Cancer (IARC) TP53 database, the APC Mutations Database, the International Society for Gastrointestinal Hereditary Tumors' MLH1 database, and the Multiple Endocrine Neoplasia Type 2 RET Database were all used to review cases in this report. Fourth, proof of the variant's impact on the biochemical activity of the protein and/or cellular pathway is compiled using the literature and/or locus-specific databases[41].

5. Gene-drug Pairings, According to Evidence-based Dose Adjustment Guidelines

Implementing gene-drug pairs with marginal or negative cost-effectiveness may not be worthwhile, such as when genotyping is costly or time-consuming, variant frequency is low, the clinical implications of inadvertent toxicity are minimal, or there are simpler

alternatives to avoid serious toxicity. The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group collaborated to establish pharmacogenomics-guided prescribing guidelines based on rigorous evidence evaluation[42]. The Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group guidelines for dose modification offer specific instructions for each significant DPYD mutation based on projected metabolic impairment[43-45] DPYD variant carriers have major clinical implications and high management costs, although having a lower frequency than other gene-drug combinations.6

Upfront DPYD genotyping is cost-effective and has become standard of care in countries such as the Netherlands, France, Switzerland, Germany, and the United Kingdom[46-49].

6. Role of Pharmacogenomics in Adverse Drug Reactions

The pharmacogenomic machinery includes genes that encode enzymes and proteins involved in drug targeting and processing, as well as epigenetic components that regulate gene expression[49]. The pharmacogenomic response to medicines involves five key groups of genes: (i) Genes linked to illness pathophysiology; (ii) Drug action mechanisms (enzymes, receptors, transmitters, messengers); and (iii) Drug metabolism enzymes (phase I-II)[50]. ADRs can be classified into two types: type A and type B (Table 1). Type A reactions are prevalent, predictable, and can affect any individual.Type B ADRs are rare and unpredictable, occurring only in sensitive individuals [51]. Type A responses are the most common, affecting 25–45% of patients. The drug's known primary and/or secondary pharmacological activities are exaggerated, dose-related, and potentially avoidable [52].Type B reactions, also known as idiosyncratic drug reactions, do not have a clear dose-response connection in susceptible individuals and cannot be explained by the drug's pharmacology. These are sometimes unidentified until the medicine is introduced and are linked to higher mortality rates[53].

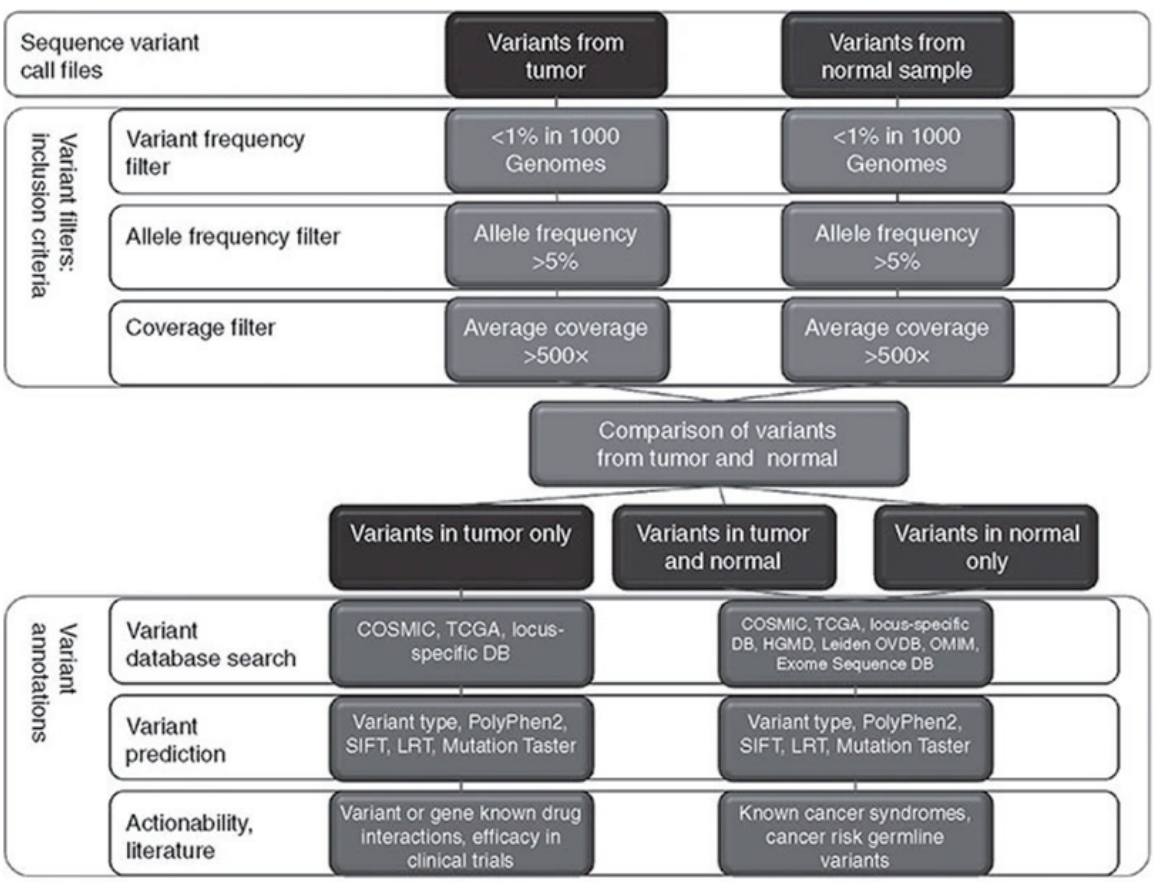

Figure 3. Overview of the somatic variant assessment protocol

Table1. Characteristics of type A and type B adverse drug reactions

Characteristics	Type A	Type B
Dose dependency	Usually show a good relationship	No simple relationship
Predictable from known pharmacology	Yes	Not usually
Host factors	Genetic factors might be important	Dependent on (usually uncharacterized) host factors
Frequency	Common	Uncommon
Severity	Variable, but usually mild	Variable, proportionately more severe
Clinical burden	High morbidity and low mortality	High morbidity and mortality
Overall proportion of adverse drug reactions	80%	20%
First detection	Phases I–III	Usually phase IV, occasionally phase III
Animal models	Usually reproducible animals	No known animal models

7. Pharmacogenetic Studies of Drugs

The "Human Genome" project paved the way for molecular medicine, a field that focuses on genetic markers. Genetic markers are unique point nucleotide polymorphisms that reflect an individual's features. The increasing availability of data on SNPs and other genetic alterations contributes to understanding the genome[54-55].

•Poor metabolism (PM) refers to alleles with altered genes that affect key enzymes involved in drug metabolism and activity. Mutations can result in inadequate enzyme synthesis or inactive gene products, leading to decreased or even loss of enzymatic activity. Drugs processed by the same enzyme have slower elimination rates. As a result, the patient is at risk of reaching a high plasma concentration of the drug, as well as experiencing dose-dependent side effects. In this aspect, slow metabolizers require careful drug dosage selection.

•Extensive metabolizers (EM): They maintain a consistent pace of drug biotransformation. They typically have two active allelic genes, or one functional and one partially active allele.

•Intermediate metabolizers (IM) are heterozygous carriers of the mutation, with autosomal recessive inheritance. For optimal therapeutic effects, lower pharmacological dosages may be necessary.

•Ultra-fast metabolizers (UM) have enhanced gene expression due to the presence of three or more functional alleles after duplication (e.g., CYP2D6). Ultra-fast metabolizers may need a greater dose of a medicine as shown in Fig 4 [56].

8. Pharmacogenomics for Medication Therapy in Cinical Settings

Drug therapy has typically been based on the one-drug-fits-all philosophy, but this is increasingly changing. Biomarkers are increasingly being used to personalize therapy and monitor response rates. Pharmacogenetic biomarkers include genetic polymorphisms in CYP enzymes (oxidative metabolism), UTG1A1 (glucuronidation), VKORC1 (warfarin target), EGFR (growth factor receptors driving cancer), NAT2 (acetylation), MDR1 and BCRP (efflux transporters), among others. Pharmacogenetics first focused on drug metabolizing enzymes and membrane transporters, which play a significant role in controlling drug delivery and duration in the body. Genetic indicators can optimize doses and help minimize toxicity in certain drugs, such as antipsychotics that require CYP2D6 for clearance. Genetic biomarkers associated to drug receptors and signaling pathways may influence pharmacological class selection. Although this technique is gaining traction in cancer treatment, our understanding of other therapeutic areas remains restricted[57]. Healthcare providers should adapt pharmacotherapy based on a patient's genotype, which can be determined using drug labels and guidelines. However, the majority of patients do not yet know their clinically important genotypes. Due to a lack of data supporting upfront panel-based genotyping, PGx is

1 Gene–drug pairs, in accordance with evidence-based dose adjustment guidelines*

Drug class	Drug	Gene
Anticancer agents and immunosuppressants	Azathioprine	*TPMT*
	Mercaptopurine	*TPMT*
	5-Fluorouracil	*DPYD*
	Capecitabine	*DPYD*
	Irinotecan†	*UGT1A1*
	Tacrolimus	*CYP3A5*
	Tamoxifen	*CYP2D6*
Anticoagulants and antiplatelet agents	Warfarin	*CYP2C9, VKORC1, CYP4F2*
	Clopidogrel	*CYP2C19*
Antimicrobials	Abacavir	*HLA-B*
	Voriconazole	*CYP2C19*
	Aminoglycosides‡	*MT-RNR1*
Antidepressants	Fluvoxamine‡	*CYP2D6, CYP2C19*
	Citalopram	*CYP2D6, CYP2C19*
	Nortriptyline	*CYP2D6, CYP2C19*
	Amitriptyline	*CYP2D6, CYP2C19*
	Sertraline	*CYP2D6, CYP2C19*
Anticonvulsants	Carbamazepine‡	*HLA-A, HLA-B*
	Phenytoin	*HLA-B, CYP2C9*
Statins	Simvastatin‡	*SLCO1B1, ABCG2, CYP2C9*
	Atorvastatin‡	*SLCO1B1, ABCG2, CYP2C9*
	Rosuvastatin‡	*SLCO1B1, ABCG2, CYP2C9*
Proton pump inhibitors	Omeprazole	*CYP2C19*
	Pantoprazole	*CYP2C19*
	Lansoprazole	*CYP2C19*
Anti-gout agents	Allopurinol‡	*HLA-B*
	Rasburicase‡	*G6PD*
Analgesics	Opioids‡	*COMT, CYP2D6, OPRM1*
	NSAIDs	*CYP2C9*

Figure 4. Gene-drug pairings, according to evidence-based dose adjustment guidelines

primarily used for retrospective single-gene testing to explain ineffectiveness or adverse responses. Despite decades of clinical research on genetic polymorphisms in pharmacogenes, many physicians and pharmacists are still unaware of their potential[58-60]. Molecular knowledge enables personalized treatments, perhaps lowering costs by removing unsuccessful individual medicines. Former HHS Secretary Leavitt predicted that implementing the PHC paradigm would take a generation due to its complex integration of multiple components. The federal program will become a collaborative effort between private sector and academia. The PHC framework's architects will collaborate with physicians, pharmacists, health professionals, and patients to maximize its potential (see Figure 5)[61].

9. Diagnostic & Prognostic Testing

Clinical trials including diagnostic and/or prognostic biomarkers are on the rise. One technique used in customized treatment decisions is to find biomarkers that are associated with patient treatment response and outcomes. The number of therapeutic trials using predictive biomarkers has increased tenfold over the last five years. With several notable developments in targeted medicines over the last decade[62-66]. Cancer patient treatment has greatly improved. Early successes have included trastuzumab in breast cancer and imatinib in chronic myelogenous leukemia (CML). Trastuzumab, a targeted therapeutic medication, is more effective when used with chemotherapy for patients with HER2-positive early breast cancer. Trastuzumab in combination with chemotherapy was found to be effective for early HER2-positive breast cancer patients, but not for high-risk HER2-negative patients (NSABP B-31 trial excluded)[67-69].

10. Role of Pharmacogenomics and

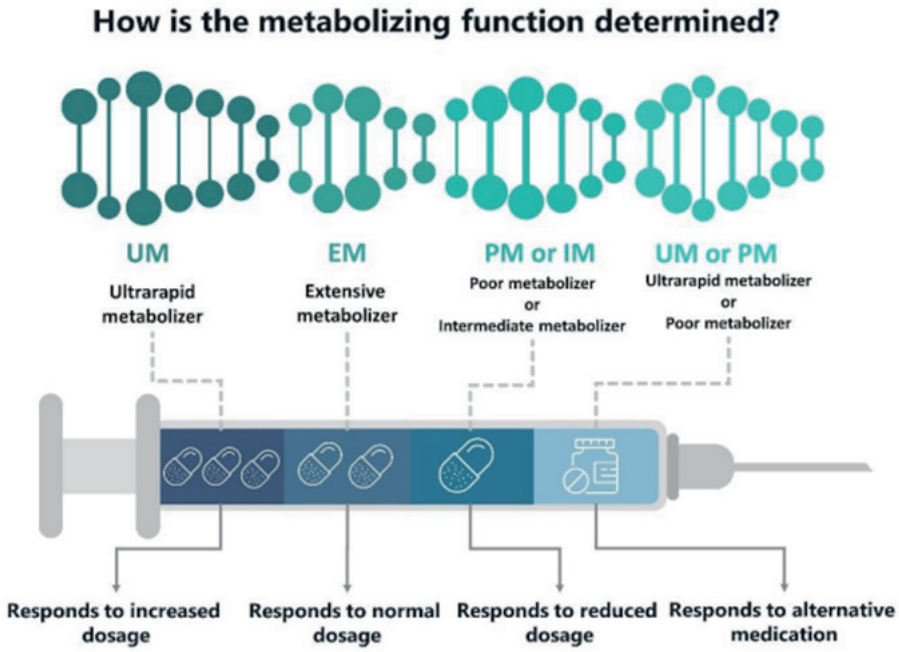

Figure 5. Genetic variation in metabolic phenotype

Pharmacoproteomics

•Advances in genomics and genetics have supplied a wealth of information, and researchers are investigating how to integrate these discoveries with people's genomes and medical histories. The completion of the Human Genome Project has prompted interest in pharmacogenomics. Pharmacogenomics is a scientific discipline that studies the ability to screen for changes in genes and their expression using molecular diagnostics and then treat with targeted drugs[70].

•Individual genetic profile can predict illness risk and treatment response, leading to more tailored therapy and better knowledge of disease pathophysiology. According to a survey of hospitalized patients, adverse medication responses are the sixth largest cause of death, emphasizing the importance of proper treatment[71].

•Pharmacoproteomics, with pharmacogenomics and pharmacogenetics, plays a crucial role in developing tailored treatments. Pharmacoproteomics utilizes proteome methods for drug discovery and development, providing a better functional depiction of individual variation compared to genotyping. Protein chips and other proteomic technologies are expected to play a larger role in clinical diagnosis in the coming years[72].

11. The Complex System of Drug Metabolism

Orally ingested medications may pass through the upper GI tract and small intestine before reaching the large intestine, where they come into contact with the hundreds of bacteria species that live in the human gut. Complex drug-microbial interactions primarily occur in the colon. Drugs can modify the intestinal milieu, microbial metabolism, or bacterial growth, all of which affect the composition and function of the microbial community. In contrast, the gut microbiome can directly engage in the chemical modification of medicines (Fig. 6). Drug metabolism in the host happens mostly in the liver and is separated into two stages of reaction: modification and conjugation. It has been recognized, however, that the chemical alterations carried out by gut bacteria differ significantly from these hepatic activities[73]. Drug metabolites are delivered to targeted tissues after metabolism in the gut and/or liver, or they are eliminated by the kidneys into urine or by the liver via the biliary system back into the gut lumen. In the gut, medicines or their drug metabolites may be exposed to bacterial metabolism (e.g., deconjugation) and (re)absorption[74]

12. Medication Perturbs the Gut Microbiota

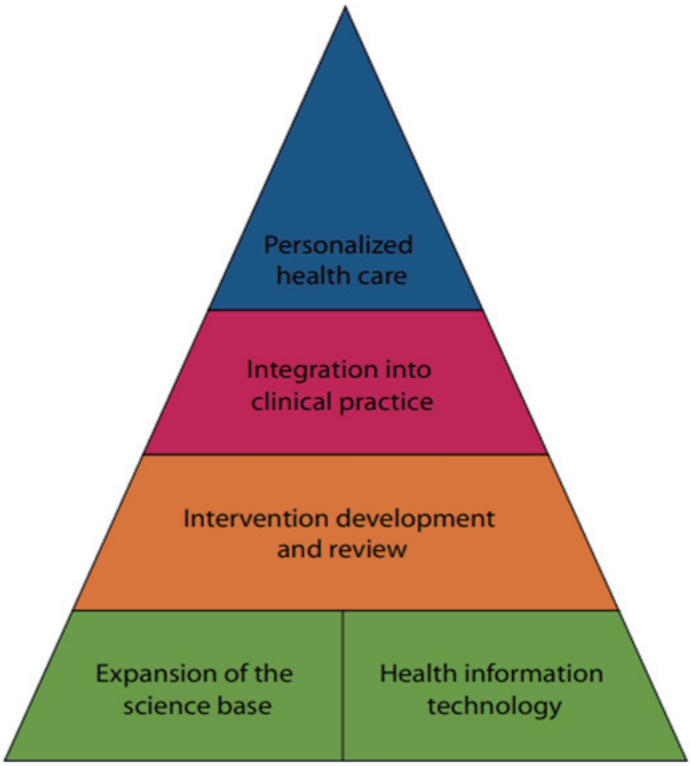

Figure 6. Personalized health care building

Drug's alteration in microbial makeup and function can contribute to its overall effects on the host, raising concerns about drug administration. Antibiotics' effects on the gut microbiome are the most investigated. Antibiotic-induced dysbiosis in the gut microbiome can increase susceptibility to infections, disrupt immunological homeostasis, deregulate metabolism, and obesity[75]. Furthermore, it is a leading cause of Clostridium difficile infection, a serious intestinal inflammation caused by the overgrowth of this bacteria, which affects around 124,000 individuals every year and causes 3,700 deaths in Europe[76]. Aside from antibiotics, a number of research in humans and mice have recently examined the effect of other regularly used medications on the gut flora. This includes our metagenomics analysis in a Dutch population cohort of 1,135 samples, where we discovered 19 medications that altered gut microbial composition. While the majority of the current findings are association-based, the identification of a causal impact of proton pump inhibitors (PPIs), which are used to treat gastro-oesophageal reflux and heartburn, and the anti-diabetic drug metformin on gut microbiome composition provides firm evidence that change in gut microbiome should be considered when evaluating drug safety, and that drug use can also confound microbiome analysis (Fig 7) [77].

13. Conclusion

Examining the variation profiles of several people is essential for identifying genetic biomarkers for certain illnesses. Even while NGS is becoming more affordable, it is still beyond of reach for several nations. Genomic analysis will become more affordable as technology and informatics continue to advance. It is anticipated that microarrays and bead arrays, two forms of inexpensive genotyping technology, would become more prevalent in therapeutic settings. Sequencing errors in homopolymer regions, which may happen on certain systems, are presently limiting NGS. Sequence data analysis is laborious and requires expertise in bioinformatics. Tight regulations are necessary to ensure the safety and effectiveness of drugs before they can be commercialized. A more tailored approach to medicine prescription is possible with the use of NGS technology, which can analyze genetic profiles. By customizing pharmaceutical prescriptions to reduce adverse effects and overconsumption, pharmacogenomics is an essential component of individualized therapy. New drugs that are safer, more effective, and less expensive may be developed using

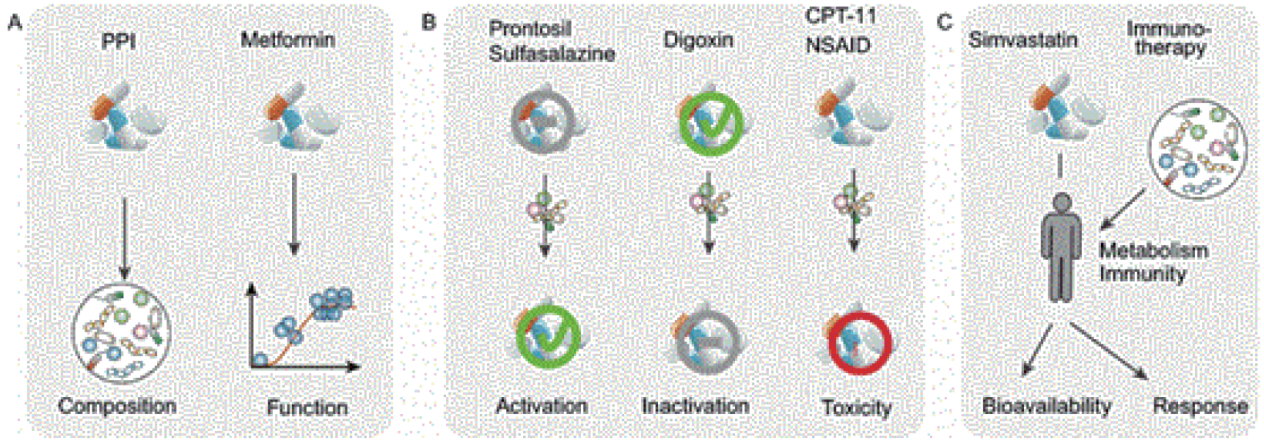

Figure 7. Sites and types of reactions for drug metabolism

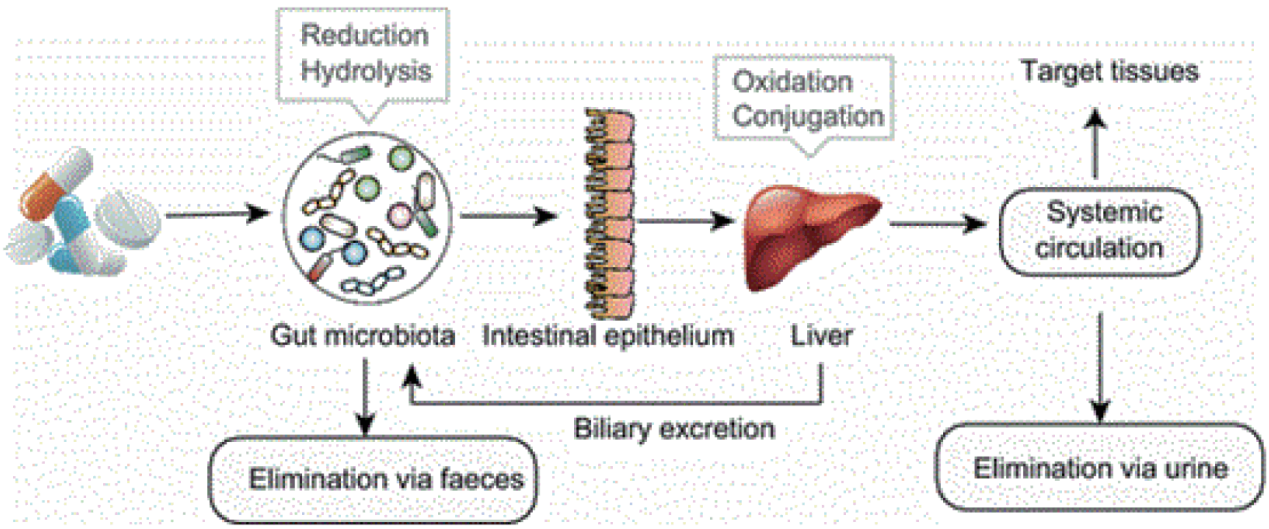

Figure 8. Drug Microbe Effect

genetic data. To better understand the underlying causalities and processes, a systems-based approach and specialized drug testing methodologies are needed. This is because there is a broad variety of microbial composition, and microbes play varied roles in the host. Additionally, drug-diet-microbe-host interactions are intricate. New, state-of-the-art technologies in areas such as bacterial culturomics and individualized organs-on-chips, along with the exponential expansion of databanks and biobanks that store vast quantities of information about a single person, will allow personalized medicine to enter its next stage.

Conflict of interest

There are no conflicting interests, as the authors have stated.

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