Chapter 13
Pharmacogenomics: Clinical Perspective, Strategies, and Challenges

Dev Bukhsh Singh

Abstract Pharmacogenomics (PGx) defines the genetic basis of variability among individuals in response to drugs. It is an emerging discipline of medical science and is now a challenging and applied area of medical research. Several factors influence the efficacy and toxicity of drugs such as environmental factors, age, weight, gender, liver and kidney function, and applied drug therapy. Another crucial factor that influences the drug response of a patient is the genetic makeup of the patient. Polymorphism affects the drug efficacy, bioavailability, and toxicity. Human Genome Project (HGP) has provided a foundation for PGx study by identifying genes related to a disease. PGx knowledge derived from genetic profiling and associated drug response must be translated into clinical applications. A drug label contains information about PGx biomarker and drug related to a therapeutic area and also provides specific information for safe and effective medication based on a biomarker. PGx drugs have improved therapeutic response and also avoid events of adverse drug reactions (ADRs). There are some important ethical, social justice, and economic issues related to PGx which create hurdles in the drug development via PGx. The objective of this chapter is to discuss the basic principle of PGx and its application and also to put forward the ethical, social, technological, and economic challenges in the way of PGx. In spite of many challenges, it is expected that PGx may offer significant promises toward the goal of personalized medicine in the future.

Keywords PGx • Polymorphism • Drug development • Clinical trial • Biomarker • Personalized medicine

D.B. Singh (✉)
Department of Biotechnology, Institute of Biosciences and Biotechnology, Chhatrapati Shahu Ji Maharaj University, Kanpur 208024, Uttar Pradesh, India
e-mail: answer.dev@gmail.com

D.-Q. Wei et al. (eds.), *Translational Bioinformatics and Its Application*, Translational Medicine Research, DOI 10.1007/978-94-024-1045-7_13

13.1 Introduction

PGx is the study of how genes affect drug response within a person or population. This is an emerging field which combines pharmacology and genomics to find a safe and effective treatment for a disease based on the genetic makeup of an individual. The long-term goal of PGx is to help doctors in selecting the drug and dosage best suited for each patient, based on patient's gene, an environment, lifestyle, and other characteristics. The major objective of PGx is to identify all the genetic and epigenetic differences that cause phenotypic variations in patient's response to drug therapy (Hess et al. 2015). Most of the drugs that are currently available are not genome specific and also do not have the similar response to each individual. These drugs generate three possibilities after treatment: positive response, adverse reactions, and no response to a population (Fig. 13.1). PGx promises a dramatic improvement in drug safety and efficacy. HGP played a very important role in learning the significance of inherited differences in genes on individual's drug response to medication. Patient's response to a drug depends on pharmacokinetics and pharmacodynamics. Pharmacokinetic effects are due to differences in absorption, distribution, metabolism, or excretion of the drug. The inappropriate concentration of drugs and metabolites can result in toxicity. In contrast, pharmacodynamics defines the efficacy of drugs among individuals despite the presence of an effective concentration of drug at the site of action (Wispelwey 2005).

The goal of PGx is to develop genetic-based strategies that will optimize the therapeutic outcomes. PGx uses the differences in genetic makeup to find an effective treatment for a particular individual and also avoids the chances of ADR. PGx approach has been used for cancer, anticonvulsant, anti-infective, cardiovascular, opioid, proton pump inhibitor, and psychotropic drugs, as well as other types of therapies. The use of PGx is quite limited, but new approaches are

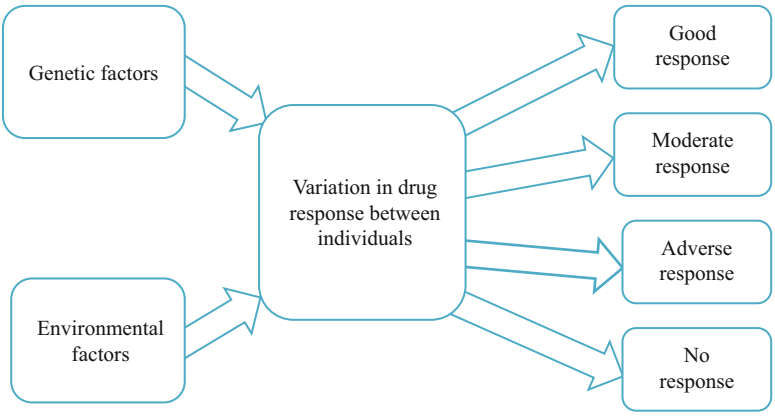

Fig. 13.1 Responses of a drug in traditional treatment

under study in clinical trials. In the future, PGx will offer a potential and effective medication to a wide range of health problems, including cancer, AIDS, Alzheimer's disease, and other fatal diseases (Genetic Home Reference n.d.). ADRs lead to a large number of injuries and deaths every year. PGx tests decrease the possibility of ADR. It also reduces the need for trial and error treatment to find the best therapy. Codeine is an effective painkiller, and it acts after its conversion to morphine, which needs to be detoxified and excreted. For example, codeine may have a toxic effect because of the high amount of morphine produced and/or impairment of excretion. Individual genetic differences, as well as prescribed drugs, affect the related metabolic pathways with clinical implications. Adverse drug events result in high cost and experimenting with treatments is expensive. Thus, PGx test reduces the overall cost for patients and physicians significantly.

Genetic basis of drug response enables us to understand the most critical aspects of drug action, improves drug safety, and makes it easier to prescribe the right dose for each person. PGx supports the drug development process which could be achieved through a more rationalized, safer, and less expensive clinical trial process. Drugs that suit to an individual with a particular genetic profile could be marketed only for those with that genetic makeup, while drugs previously in use could be recommended to the patient or limited population for whom they are safer. Differences between individuals can affect drug absorption, metabolism, toxicity, or activity. Therefore, while one treatment may work well for one individual, the same may cause adverse effects to other individuals (Kitzmiller et al. 2011). Currently, the majority of drug prescriptions are based on clinical factors such as patient's age, weight, sex, and liver and kidney function. For a small subset of drugs, scientists have identified the genetic variations that affect people's response to a drug. The Food and Drug Administration (FDA) of the United States includes the PGx information such as dosage guidelines, possible side effects, or difference in effectiveness for people with certain genomic variations for more than 150 medications (U.S. FDA n.d.).

PGx utilizes the variations in genes for proteins or enzyme that affects the response of a drug. Such proteins include a number of liver enzymes that convert drugs into their active or inactive forms. Even small variations in the genetic composition of these enzymes can have a big impact on a drug's safety or effectiveness. A gene may exist in many forms/versions, many of which vary by only a single difference in their DNA sequence or some may have larger changes. Most of these genetic variants do not influence the drug responses. Some patients may have much more copies of a gene. Those with extra copies of this gene manufacture an overabundance of enzyme molecules and show a different response to treatment with a drug (NIH, NIGMS n.d.). Pharmaceutical companies are using the PGx knowledge to develop and market drugs for patients with specific genetic profile. PGx also raises a lot of ethical issues. There is a need to protect informed consent and confidentiality and to promote justice and equity both nationally and globally. There is a need of a public policy related to PGx for the betterment of individual and society. The potential benefits of PGx should not be underestimated even from an ethical point of view.

13.2 Genetic Polymorphism

Studies have shown that about 85% of human diversity at short tandem repeat (STR) and restriction fragment length polymorphism (RFLP) autosomal loci is due to differences between individuals of the same population, whereas differences between populations of the same continent account for 5–10% (Romualdi et al. 2002). A study based on more than 350 microsatellites from a global sample of humans showed that individuals could be grouped according to their continental origin (Serre and Pääbo 2004). Results indicated that the pattern seen is one of the gradients of allele frequencies that extend over the entire world and also disqualify the assumption that major genetic discontinuities exist between different continents or races. Human genetic variation is based on patterns of gene flow and genetic drift (Jorde and Wooding 2004). Therefore, ancestry or racial study may prove useful in the biomedical testing, but the results directly associated with disease-related genetic variation will be more accurate and beneficial. CYP2D6 allele frequency varies among racial groups. In European Caucasians and their descendants, the functional group of alleles is predominant, with a frequency of 71% (Bradford 2002). The alleles which encode for no or reduced functioning will affect the activity of the CYP2D6-mediated drug. Therefore, allele-related studies are necessary to assure the optimal dosing recommendations.

HGP has provided a foundation for PGx study by identifying genes related to a disease. Genetic information derived from genomic research must be translated into clinical applications for the welfare of society. Most differences in drug response among individuals are not caused by mutation of a single gene but by the altered function of genes. Variations in absorption, distribution, metabolism, and excretion (ADME) genes and the genes associated with drug targets may result in the absence of protein or the production of a protein with altered or no activity. These variations decide overall metabolism of the drug and the therapeutic index of the drug, as well as the activity of its metabolites (Nadine and Theresa 2008). The clinical association of a genetic variation can be related with a disease. Cyclooxygenases are the key enzymes in several physiopathological processes. Genes coding for these enzymes (*PTGS1* and *PTGS2*) are highly variable, and variations in these genes cause the risk of developing several diseases and ADR. Major variations in the *PTGS1* and *PTGS2* genes, allele frequencies, functional consequences, and population genetics have been analyzed (Agúndez et al. 2015). The most salient clinical associations of *PTGS* gene variations are related to colorectal cancer and stroke. Genes responsible for a clinical outcome can be identified by correlating variability in genotype with phenotypic differences.

The study of genetic variants associated with cancer or any disease helps in early detection of disease and also opens the way for personalized cancer therapy. In recent years, the GWAS studies have provided information about many genetic variants in cancer. For example, the presence of genetic variants rs1447295 and rs6983267 on 8q24 contributes to prostate cancer in Europeans (Yeager et al. 2007). These variants provide a useful biomarker for diagnosis and therapeutic

categorization. The systematic cataloging of genetic variants may provide the information of pathways controlling the cellular activities in cancer (Cho 2010). Genetic variants can be more clinically useful if they are combined with the family history records of the disease. New diagnostic test and therapeutic strategies can be developed on the basis of biochemical targets to control the disease. Rare genetic variants are too rare to be identified by GWAS and they have large effect on disease risk (Cirulli and Goldstein 2010). The 1000 Genomes Project has identified many genetic variants at lower frequencies. Some examples of polymorphism and its effect on metabolism and therapeutic role have been discussed here.

13.2.1 Polymorphism in miRNA

MicroRNAs (miRNAs) are small, single-stranded, 19–21 nucleotide long nonprotein-coding RNA molecules. miRNAs act as negative regulators of gene expression through binding to their target mRNAs and consequently lead to mRNA cleavage or translational repression (Bartel 2004). The miRNAs regulate the expression of roughly 10–30 % of all human genes, including the genes related to cell differentiation, proliferation, and apoptosis (Berezikov et al. 2005). miRNA may contribute to cancer development with changes in the miRNA's properties and/or maturation process. A study was performed to validate the potential association between the four common SNPs (miR-196a2C.T, rs11614913; miR-146aG.C, rs2910164; miR-499A.G, rs3746444; miR-149C.T, rs2292832) and the risk for developing cancer (He et al. 2012). The results of this study indicated that the rs11614913TT genotype is significantly associated with a decreased risk for colorectal cancer and lung cancer. The rs2910164C allele is associated with decreased risk for cervical cancer, esophageal cancer, prostate cancer, and hepatocellular carcinoma. SNPs in miRNA may prevent the pathogenesis of some cancers, and some SNPs may also increase risk for cancer.

13.2.2 Urate Transporter 1 (URAT1) Polymorphisms

Genetic variation is routinely seen in all drug targets. African populations show more genetic variation than Asian (Gurdasani et al. 2015). In most cases, these polymorphisms do not alter the encoded amino acid and probably have no functional effect. Approximately 75% of drug targets sequenced have at least one amino acid changing genetic variant and >35% having more than three variants (McHale 2008). Sequence polymorphism reflects the variability in chemical target interactions, but the real effect can only be tested in vitro or in clinical trials. In a polymorphism-related study, the effect of urate transporter 1 (URAT1) polymorphisms in the hypertensive patients with hyperuricemia and the uricosuric action of losartan therapy were explored. Results suggest that URAT1 rs3825016 and

rs1529909 polymorphism affects the uricosuric action of losartan (Sun et al. 2015). Polymorphism affects the drug efficacy, bioavailability, and toxicity.

13.2.3 Opioid Receptor Polymorphism

Knowledge of polymorphism is important as a specific type of polymorphism is responsible for a particular characteristic which might not be exhibited by other types. The pharmacologic actions of opioids are due to their interaction with the opioid receptors (G-protein-coupled receptors) located in the brain and spinal cord (Feng et al. 2012). Three subtypes of opioid receptors are mu-opioid receptors, kappa-opioid receptors, and delta-opioid receptors. The mu-opioid receptor is the primary site of action of opioid analgesics including morphine, fentanyl, and methadone. More than hundred polymorphisms are reported for the human mu-opioid peptide receptor gene. These polymorphisms are associated with both agonistic and antagonistic opioid effects. Studies have shown that *Gpr88*, *Ttr*, *Gh*, and *Tac1* mRNAs were altered in mice exposed to chronic stress (Ubaldi et al. 2015). These transcripts represent a biomarker and therapeutic targets for diagnosis and can also help in treatment of chronic stress-associated disease in humans.

13.2.4 The HapMap Project

The International HapMap Project was initiated in the year 2002 (International HapMap Project n.d.). The goal of this project was to map the common patterns of DNA sequence variation in the human genome. An international consortium was involved in the mapping of these patterns across the genome by determining the genotypes of sequence variants, their frequencies, and the degree of association between them. The HapMap guides the discovery of sequence variants that affect common disease. The HapMap facilitates the development of diagnostic tools and also helps in drug target selection for therapeutic intervention. The HapMap enhances our understanding of the hereditary factors involved in health and disease. The International HapMap Project has much in common with the Human Genome Project. The Human Genome Project covered the sequencing of the entire genome, including the 99.9% of the genome where all human beings are identical in genetic makeup (International HapMap Consortium 2003). The HapMap project characterizes the common patterns of DNA sequence within the 0.1% where individuals differ from each other.

13.2.5 The 1000 Genomes Project

The data from 1000 Genomes Project is publically available through the 1000 Genomes Project website and dbSNP. This project was completed between 2008 and 2015 and provides the largest public catalog of human variation and genotype data (IGSR: The International Genome Sample Resource n.d.). The goal of this project was to find most genetic variants with frequencies of at least 1% in the population. The International Genome Sample Resource (IGSR) was set up to ensure the future usability and accessibility of data from the 1000 Genomes Project. The goal of IGSR is to expand the data collection to include new populations and ensure the future usability of the 1000 Genomes reference data (IGSR n.d.).

13.2.6 PGx Biomarkers and Drug Labeling

PGx plays an important role in identifying responders and nonresponders to a drug, avoiding adverse events, and prescribing drug dose. Biomarkers include genetic or somatic gene variants, changes in expression level, functional irregularities, and chromosomal abnormalities. Drug labeling provides information about genomic biomarkers and can describe (1) drug exposure and clinical response variability, (2) risk of ADR, (3) genotype-specific dosing, (4) mechanism of drug action, and (5) polymorphic drug target and disposition genes. FDA-approved drugs with PGx information in their labeling are listed in Table 13.1. The labeling for the products includes specific information for safe and effective medication based on biomarker information.

EGFR has been approved as a biomarker in the therapeutic area of oncology (lung cancer). The efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is superior to that of cytotoxic chemotherapy in advanced non-small cell lung cancer (NSCLC) patients (Zhang et al. 2014). The efficacy of EGFR-TKIs (gefitinib, erlotinib, and afatinib) differs between exon 19 deletion and exon 21 L858R mutations. The L858R mutation (exon 21) results in an amino acid substitution at position 858 in EGFR, from a leucine (L) to an arginine (R) (My Cancer Genome n.d.). Patients with EGFR-mutated tumors display a longer progression-free survival (PFS) on EGFR-TKI therapy. It has been reported that patients with EGFR exon 19 deletions were associated with longer PFS compared with L858 mutation at exon 21 (Zhang et al. 2014). The investigators should consider the sensitive EGFR mutation as an important factor in clinical studies regarding target therapy. After a demonstration of a genetic association with response phenotype, there is the need to validating the biomarker for a diagnostic test.

Cytochrome P450 (CYP) enzyme polymorphisms are a determining factor in a patient's ability to respond to different drugs (Lynch and Price 2007). CYP enzymes metabolize the drugs within the endoplasmic reticulum of liver cells,

Table 13.1 List of some PGx biomarkers in drug labeling

Drug	Therapeutic area	Biomarker	Referenced subgroup	Labeling section
Abacavir	Infectious diseases	HLA-B	HLA-B*5701 allele carriers	Boxed warning, contraindications, warnings and precautions
Afatinib	Oncology	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) positive	Indications and usage, dosage and administration, adverse reactions, clinical pharmacology
Aripiprazole	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and administration, clinical pharmacology
Busulfan	Oncology	BCR-ABL1	Philadelphia chromosome negative	Clinical studies
Carvedilol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Drug interactions, clinical pharmacology
Clobazam	Neurology	CYP2C19	CYP2C19 poor metabolizers	Dosage and administration, use in specific populations, clinical pharmacology
Glipizide	Endocrinology	G6PD	G6PD deficient	Precautions
Celecoxib	Rheumatology	CYP2C9	CYP2C9 poor metabolizers	Dosage and administration, use in specific populations, clinical pharmacology
Chlorpropamide	Endocrinology	G6PD	G6PD deficient	Precautions
Cisplatin	Oncology	TPMT	TPMT intermediate or poor metabolizers	Clinical pharmacology, warning, precautions
Diazepam	Psychiatry	CYP2C19	CYP2C19 poor metabolizers	Clinical pharmacology
Mafenide	Infectious diseases	G6PD	G6PD deficient	Warnings, adverse reactions
Omeprazole	Gastroenterology	CYP2C19	CYP2C9 poor metabolizers	Drug interactions

U.S. FDA (n.d.)

and waste is excreted through urine. Most phase I metabolizing enzymes belong to CYP family (CYP3A4, CYP3A5, CYP2D6, CYP1A1, CYP1B1, and CYP2E1) and convert a wide range of substrates into more water-soluble form (Yiannakopoulou 2015). The polymorphisms of transporter enzymes, such as the OATP family of transporters, have also been linked to differences in the pharmacokinetics of drug absorption. For example, a single nucleotide polymorphism (SNP) in the SLCO1B1 gene, which encodes the OATP1B1 enzyme, leads to impaired absorption of statins (Kalliokoski and Niemi 2009). Recent studies have highlighted the role of

CYP2C19 polymorphism for the action of clopidogrel, whereas the CYP2C9 polymorphism has a role in anticoagulant treatment (Sim et al. 2013). Furthermore, the analgesic and side effect of codeine is related with CYP2D6 polymorphism, and CYP2D6 genotype influences the breast cancer recurrence during tamoxifen treatment. In another study, the effect of polymorphisms in *CYP2C9* and *CYP2C8* and gender on the pharmacokinetics of the enantiomeric (R, S) forms of ibuprofen was studied (Ochoa et al. 2015). The *CYP2C9* polymorphisms and gender affect the pharmacokinetics of *S*-ibuprofen and *R*-ibuprofen. *CYP2C8* polymorphisms do not have a significant role on the pharmacokinetics of ibuprofen. Polymorphism affects drug metabolism and is also responsible for the diverse response of the same drug to different individuals. An incidence of drug-induced toxicity also depends on polymorphism.

13.2.7 Effect of Age, Sex, and Other Factors on Drug Response

Many other factors such as age, sex, smoking or alcohol intake, intake of multiple drugs, past history of ADR, presence of other diseases, pregnancy, breastfeeding, kidney problem, and the liver function also affect the drug response (Alomar 2014). Understanding of these factors on drug response enables healthcare professionals to prescribe the most appropriate medication for a particular patient. Both very young and very old individuals are more vulnerable to ADR than other age groups. Because of all age-related changes, many drugs stay much longer in the body of old-age person than younger person's body and increase the risk of side effects (Klotz 2009). Genetic, hormonal, and physiological differences between male and female affect the prevalence, incidence, and severity of diseases and responses to therapy (Soldin et al. 2011). In an age- and sex-based study of cortisol plasma level in normal control and Alzheimer's diseases (AD), a significant difference in cortisol plasma levels between female AD patients and age-matched female controls and between female and male AD patients has been reported (Leblhuber et al. 1993). Important pharmacokinetic and pharmacodynamic changes occur with advancing age. Pharmacokinetic changes include a reduction in renal and hepatic clearance and an increase in the level of lipid-soluble drugs, whereas pharmacodynamic changes involve altered sensitivity to several drugs such as anticoagulant, cardiovascular, and psychotropic drugs (Mangoni and Jackson 2004).

13.2.8 Herb-Drug and Drug-Drug Interactions

Environmental chemicals, coadministered drugs, dietary constituents, tobacco smoking, and alcohol intake are known to induce or inhibit drug-metabolizing

enzymes and drug transporters (Ma and Lu 2011). The factors alter drug efficacy, induce drug-drug and drug-chemical interactions, and result in drug side effects. Herbs in combination with therapeutic drugs result in herb-drug interactions. Herb-drug interactions may lead to serious clinical consequences. *Ginkgo biloba* (ginkgo) causes bleeding when combined with warfarin or aspirin, raises the blood pressure when combined with a thiazide diuretic, and may cause coma when combined with trazodone in patients (Hu et al. 2005). Herbs should be labeled to alert patients when used in combination with a drug. A drug-drug interaction (DDI) involves pharmacokinetic or pharmacodynamic mechanisms. Adverse drug reactions may occur due to DDIs, and health service providers are often unaware of the ADR of certain drug combinations (Magro et al. 2012). DDIs can lead to ADR, particularly in cancer patients, because of polypharmacy and age-related organ dysfunction (Chan et al. 2009). The number of clinically relevant DDIs is probably low. In most cases, DDIs may be responsible for a substantial number of hospital admissions (Becker et al. 2005). Specifically, pharmacists should have good knowledge of combinations of drugs that may cause serious DDIs. The pharmacokinetics and pharmacodynamics of many drugs are well known, but the role of coadministered herbs has not been well explored due to complex components of herbal products (Zuo et al. 2015). The pharmacokinetics and pharmacodynamics of drug-drug and herb-drug interactions cannot be ignored. The safety of coadministration of herbs together with drug should be kept in mind. These interactions need to be addressed by conducting the high-quality scientific research.

13.3 PGx Testing and Drug Discovery Process

This section describes PGx studies performed on patients with a particular disease and presents the major outcome of these studies (Fig. 13.2). The genome-wide association study (GWAS) is extensively used to analyze hundreds of thousands of SNP by high-throughput genotyping. In addition to the candidate gene approach, the GWAS approach is utilized to investigate the determinants of antidepressant response to therapy (Lin and Lane 2015). PGx has shown less impact on human health than initially expected. One reason for this is that many diseases' and patients' response to the drug treatments is affected by both genetic and environmental factors. Pure genomics should also consider the role of environmental elements (Everett 2015). Pharmacometabolomics describes the role of both genetic and environmental influences on physiology. It is concerned with the study of drug effects through the analysis of predose, biofluid, and metabolite profiles. Polymorphisms that are clinically relevant show population-specific allele frequencies. Fifteen polymorphisms from 12 genes have been assessed in 81 Peruvian and 95 Mexican individuals (Marsh et al. 2015). Six polymorphism frequencies differed significantly between these two populations.

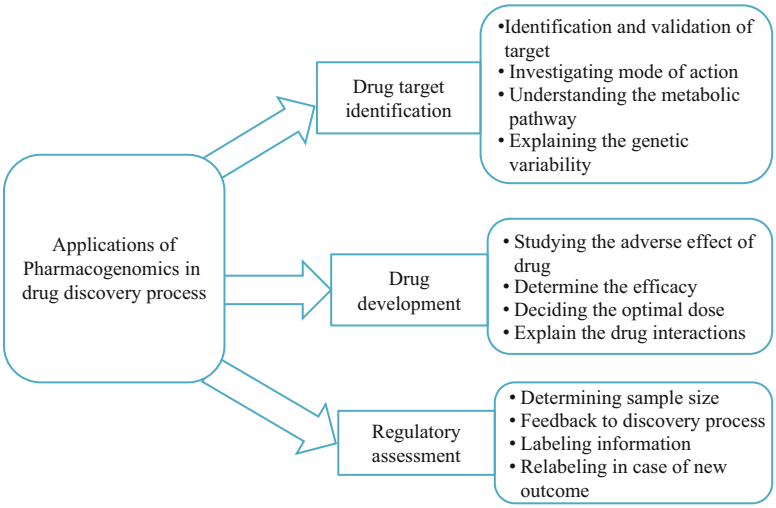

Fig. 13.2 Applications of pharmacogenomics across the drug discovery process

13.3.1 Adverse Drug Reactions and Hypersensitivity

Interindividual genetic differences are important causes of ADRs and lack of drug response. The majority of phase I and phase II drug-metabolizing enzymes are polymorphic and responsible for varying drug response (Ingelman-Sundberg and Rodriguez-Antona 2005). GWAS related to drug response and genes encoding drug-metabolizing enzymes have extracted knowledgeable information for variation in drug response and drug metabolism. For example, PGx markers in the HLA-coding genes are associated with drug hypersensitivity of multiple drugs. The HLA-B*5801 allele was significantly associated with the risk of severe cutaneous ADRs (cADRs) in the Han Chinese, Korean, Thai, Japanese, and European populations (Jarjour et al. 2015). All SNPs identified in GWAS of common variants are also located in or nearby HLA-B*5801. Five specific HLA alleles that predict drug-induced hypersensitivity reactions (HSR) were tagged by seven SNPs (He et al. 2015). It was concluded that SNP tagging is a "real-time" approach to identify the specific HLA alleles associated with drug-induced hypersensitivity across diverse racial groups. The influence of SNPs has been studied on efficacy and safety of calcineurin inhibitors upon heart transplantation (Sánchez-Lázaro et al. 2015). A panel of 36 SNPs was correlated with a series of clinical parameters. Such types of studies can identify the patients at increased risk of clinical complications.

13.3.2 Lung Adenocarcinoma

There is need to expand the scope of geographic data in PGx. Lung adenocarcinoma is the most common form of lung cancer, and it begins in the tissues that lie near the outer parts of the lung. The impact of the genetic polymorphisms on the therapeutic efficacy of pemetrexed in lung adenocarcinoma patients has been investigated. The genotyping of 51 polymorphisms of 13 genes in 243 lung adenocarcinoma patients treated with pemetrexed was performed (Woo et al. 2015). Twelve polymorphisms in six genes were found statistically significant in univariate analysis. Finally, two polymorphisms (ATIC and GGH genes) were associated with therapeutic efficacy in multivariate analysis. Genetic polymorphisms have been identified for many enzymes, drug receptors, and transporters that are significant in clinical pharmacology. These polymorphisms can cause alterations in the amount, structure, binding, and/or function of these proteins and also affect the drug interaction with the target.

13.3.3 Breast Cancer

Cancer has become a great threat and challenge to public health. Breast cancer accounts for 23% of the total cancer burden and 14% of cancer deaths worldwide (Jemal et al. 2011). There is need of new diagnostic markers for the early detection and prevention of breast cancer. Many studies have shown that the pathogenesis of various tumors, including breast cancer, occurs due to suppression of apoptosis (Wang et al. 2012). The effects of Fas and FasL polymorphisms on breast cancer risk have been studied among the Chinese population. The Fas−1377GA, Fas−1377AA, Fas−670AG, Fa−670GG, and FasL−844TC genotypes have been associated with a lower risk of breast cancer (Xu et al. 2014). The genotype Fas−1377G/−670A was associated with an increased risk of breast cancer. This study also revealed that the Fas−1377GA/AA (−670AG/GG) and FasL−844CC or TC/TT genotypes were associated with a decreased risk of breast cancer. This study indicates that Fas polymorphisms may affect the breast cancer risk by regulating the soluble Fas concentration.

Tamoxifen is used for the treatment of breast cancer. Tamoxifen is not effective in all estrogen receptor (ER)-positive breast cancer patients and has side effects. CYP2D6 is an important enzyme responsible for the production of endoxifen, a potent tamoxifen metabolite (De Souza and Olopade 2011). Studies have shown that genetic variation reduces CYP2D6 enzyme activity and results in poor clinical outcome when treated with tamoxifen (Zembutsu 2015). Dose-adjustment study of tamoxifen based on *CYP2D6* genotypes suggests that dose adjustment is beneficial for the patients carrying reduced or null allele of *CYP2D6* to maintain the effective endoxifen level.

13.3.4 Acute Myeloid Leukemia

Variation in terms of efficacy and toxic side effects exists among acute myeloid leukemia (AML) patients on chemotherapy with cytarabine (Ara-C). Differentially expressed genes between Ara-C-sensitive and Ara-C-resistant samples were identified by global gene expression profiling (Abraham et al. 2015). Variations in Ara-C cytotoxicity were seen among samples from AML patients and categorized into sensitive, intermediately sensitive, and resistant groups, based on IC_{50} values. Ara-C resistance index could be a potential biomarker for AML treatment outcome and toxicity.

13.3.5 Tyrosine Kinase Inhibitors in Cancer Therapy

PGx informations are being widely used for drug discovery process and are already used in clinical practice for the treatment of many diseases. *EGFR* family of receptor tyrosine kinase regulates many metabolic, developmental, and physiological processes. In tumor cells, the tyrosine kinase activity of EGFR is dysregulated by various oncogenic mechanisms, including EGFR gene mutation and overexpression and increased gene copy number. Many mutations in the kinase domain of the *EGFR* gene provide sensitivity to tyrosine kinase inhibitors (TKIs). Most of these patients acquired resistance to EGFR inhibitors after treatment. EGFR-TKI resistance mechanisms include amplification and mutation in MET, resulting in tumor cell growth (Pérez-Ramírez et al. 2015). Therefore, MET is considered as an attractive target for anticancer therapy. MET promotes cell proliferation, scattering, invasion, survival, and angiogenesis. Because of the important role of MET in cancer development and progression, it has been recommended as potential target for cancer therapy.

In chronic myeloid leukemia, the bone marrow produces too many white blood cells. These cells crowd the bone marrow and interfere with the normal blood cell production. In an interesting case, a patient bearing a T315I-mutant chronic myeloid leukemia resistant to nilotinib was successfully treated with two cycles of omacetaxine and then with dasatinib (Venton et al. 2015). This study has suggested that eradication of the T315I mutation could be achieved without third-generation tyrosine kinase inhibitors. In the future, it is expected that other genetic markers of drug response for a disease will further improve the efficacy and safety of therapies. In vitro human cell line models may be used for PGx studies to know the clinical response and to identify mechanisms associated with variation in drug response.

13.3.6 Human Cell Line Models and Pharmacogenomics

In vitro human cell line models are used for cancer pharmacogenomics to predict clinical response, to generate a pharmacogenomic hypothesis, and to identify mechanisms associated with variation in drug response. Among cell line model systems, Epstein-Barr virus-transformed lymphoblastoid cell lines (LCLs) have been used to test the effect of genetic variation on drug efficacy and toxicity (Niu and Wang 2015). In the future, patient-specific inducible pluripotent stem cells could improve the predictive validity. The human LCLs comprise a useful model system for identifying genetic variants associated with pharmacologic phenotypes. Many GWAS for drug-induced phenotypes have been tested in LCLs, often incorporating gene expression data (Wheeler and Dolan 2012).

The large-scale genome-wide studies in both human and model systems have allowed us to understand how cell-based models help in finding an association between clinically relevant genetic and drug response (Cox et al. 2012). A genome-wide cell-based model was used to evaluate genetic variants for their contribution to cellular sensitivity to tamoxifen. This model has included multidimensional datasets, including genome-wide genotype, gene expression, and endoxifen-induced cellular growth inhibition in lymphoblastoid LCLs (Weng et al. 2013a). Genome-wide findings were further evaluated in NCI60 cancer cell lines. Furthermore, SNPs that were associated with tamoxifen-induced toxicities in breast cancer patients were identified. The cell-based models are very useful in genome-wide identification of pharmacogenomic markers.

13.4 Clinical Perspective and Implications

PGx has many advantages over traditional treatment options. The availability of low-cost genotyping methods can make PGx drugs cost-effective and affordable to poor people. Clinical and economic status should be identified under which a PGx test might be a cost-effective option for patients (Shabaruddin et al. 2015). It is considered that PGx tests are cost saving and better in improving human health than no-testing approach for the cure of a disease. Pharmacists should advise clinicians and patients on matters related to the implementation of PGx. The genetic variants evaluated in PGx include SNPs, nucleotide insertion, deletion, copy number variation, tandem repeat, and chromosomal translocation. In addition, gene expression is also commonly studied in PGx for relevancy in tumorigenesis and chemotherapy response. In PGx, drug prescription is purely based on the knowledge derived from association study between genetic profile and drug response. Basic steps and principles in the PGx approach of treatment are represented in Fig. 13.3. However, the current status of PGx in pharmacy colleges is poor and fails to produce pharmacists with the required knowledge or practical training in this discipline (Rao et al. 2015). More than 135 medications in the United States describe PGx

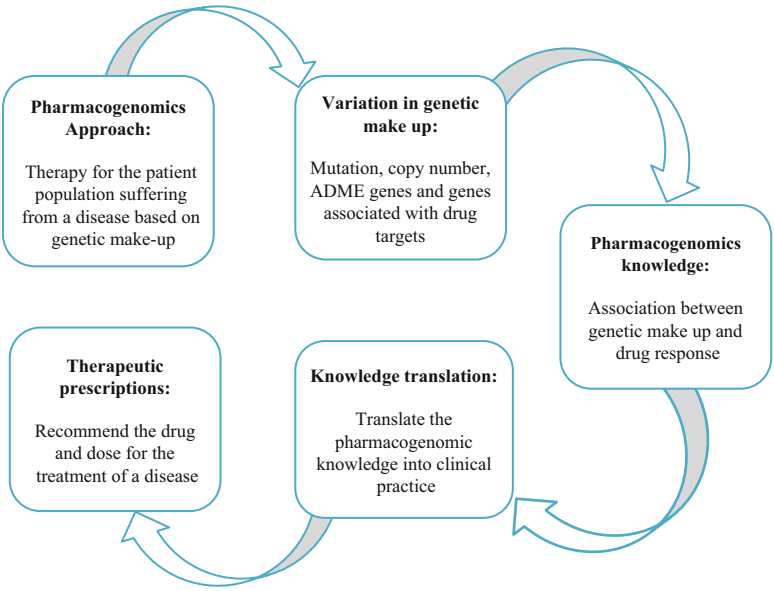

Fig. 13.3 Basic principles of PGx approach for medication

informations related to drug response or drug safety on their package inserts. Pharmacists offering PGx testing services receive billing questions specific to the laboratory tests (O'Connor et al. 2015). Pharmacists must be able to discuss these issues with the concerned patients. The goal of a pharmacist must always be to provide a high quality of result and patient care. Some testing companies offer extensive literature resources to help guide prescribers for suggesting medications.

Researchers are trying to establish an association between the response of a drug and genotype of patients suffering from that disease. Most extensive genetic studies such as GWAS, rare variant exome sequencing, copy number variant analysis, and allele-related analysis can provide an answer to the altered response of the same drug for the different individual (Cirulli and Goldstein 2010). The causal variants in single-gene disorders are necessary and sufficient to impart large effects (Marian and Belmont 2011). Knowledge of association between the genetic makeup of patients and drug response must be translated into clinical practice. If genetic variation controls the risk of drug-induced side effects, then it is recommended to identify the variants and translate them into a highly sensitive PGx test.

Understanding of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis has improved considerably over the last decades, and several PGx studies of these diseases have been carried out (Gregersen and Olsson 2009). But the clinical applications still need to be improved. A striking failure of modern medicine is an ADR which leads to death and illness in the developed world with a high healthcare cost. For autoimmune disease, several DNA-based tests are in practice to improve drug selection and dose optimization

and reduce the risk of toxicity. The "GATC" project was a nationwide project established in Canada to identify novel markers of severe ADRs in children (Ross et al. 2007). The goal of this project was to identify ADR patients, collect their DNA samples, and apply genomic studies to identify ADR-associated genetic markers. Different individuals may have a diverse response to the same drug, in terms of efficacy and toxicity. ADRs cause about 6% of all hospital admissions and account for up to 9% of hospitalization costs. Drug-induced skin injury (DISI) has been reported as the most common ADR, ranging from maculopapular eruptions to severe adverse cutaneous drug reactions (SCARs) with mortality of up to 40% (Borroni 2015). Specific genetic polymorphisms present susceptibility to different types of DISI. The cases of SCARs are now less frequent, with a low rate of morbidity and mortality.

Abnormal genes related to cancer may be inherited or acquired. Genetic changes that occur because of mutation in tumor suppressor genes, mismatch of repair genes, and mutations in oncogenes alter the cell signaling pathways and other cellular functions. Tumor-associated somatic mutations are used to identify cellular signaling pathways in tumors. Somatic mutations serve as genomic predictors of tumor response and represent a new target for drug development. A deep sequencing of 145 genes in colorectal and non-small cell lung cancers reported somatic mutations in 98% and 83% of tumors, respectively. More than half (52.5%) of colorectal cancers and 72% of non-small cell lung cancers contained at least one mutation that was associated with a specific chemotherapy approach (Lipson et al. 2012). Clinical PGx applies deep sequencing to reveal the mechanism of sensitivity or resistance to drug therapy. Drugs used in traditional cancer therapy destroy both malignant and healthy cells.

PGx drugs target the specific molecules of a pathway that is related to the division, growth, and spreading of cancer cells. One example of personalized cancer treatment is trastuzumab (Herceptin), a recombinant monoclonal antibody used for the treatment of breast cancer. Herceptin targets the human epidermal growth factor receptor 2 gene (HER2) on the tumor cell surface and induces cell-mediated cytotoxicity against the tumor cells (American Nurse Today n.d.). Leukemia is the most common cancer affecting children, accounting for 25–35% of childhood malignancies worldwide with acute lymphoblastic leukemia comprising 80% of leukemia cases. In certain leukemia patients, treatment fails due to drug resistance that is why acute lymphoblastic leukemia is the leading cause of cancer-related death in children (Ansari and Krajinovic 2007). Many advances have been made in the field of anticancer therapy. Currently, the US FDA is providing the package inserts of approximately 30 anticancer agents to include PGx information (Weng et al. 2013b). FDA recommendation and potential action needed vary among drugs. Scientific values of PGx knowledge should be used for improving therapeutic efficacy and reducing side effects. There are significant limitations to PGx discovery for anticancer therapies, because of unavailability of enough patients for both discovery and validation purpose. A clinical study is a time-consuming process, and outcomes of the clinical trial can then be used for PGx

discovery. The same is true for a validation of result, which requires enough discovery and replication studies in the literature.

Breast cancer is the most frequently diagnosed cancer in women. In breast cancer, somatic mutations in only three genes are observed with a greater than 10% incidence across primary breast cancer (Stjepanovic and Bedard 2015). Breast cancer treatment is based on the identification of expression of estrogen receptor or protein overexpression of HER2/ERBB2. HER2 amplification is tested for clinical practices related to breast cancer, as HER2-targeted therapies are approved. Genomic alternations in different types of cancer diseases can be reviewed, and genotype-based treatments can be a common practice in the future. Efforts should be made in the direction to translate the PGx knowledge to clinical application. The clozapine is used for the treatment of resistant schizophrenia patients. Agranulocytosis, an ADR, was reported in 0.8% of clozapine-treated patients, and this adverse event was not associated with dose (Verbelen and Lewis 2015). Later on, PGx evidence has established an association between HLA regions with agranulocytosis in clozapine patients, but this knowledge has not been translated into clinical practice yet.

The CYP2D6 polymorphisms have an impact on the clearance and response to a series of cardiovascular drugs. Clinical studies indicate the relationships between the CYP2D6 genotype and concentrations of drugs perphenazine, zuclopenthixol, risperidone, and haloperidol. CYP2D6 is used as an independent predictor of the outcome of tamoxifen treatment in breast cancer. Genotype testing for CYP2D6 is not customarily performed in clinical practice, and there is uncertainty regarding genotype-phenotype, gene concentration, and gene-dose relationships (Zhou 2009). Further, prospective studies on the clinical impact of CYP2D6 are required. Genetic polymorphisms of CYP, and the presence of the human leukocyte antigen (HLA)-B*1502 allele, influence drug disposition and/or response in patients (Ma et al. 2012). Pharmacokinetic and pharmacodynamic variability can be explained by polymorphism of genotype. However, conflicting evidence exists in some cases. The effect of CYP2D6 polymorphisms on codeine efficacy and toxicity is not well studied. The CYP2D6 genotyping tests are available, but its clinical utility is limited.

Lack of sufficient resources, lack of knowledge provider, and ethical, legal, and social issues are major limitations and challenges in the implementation of PGx testing for clinical application. Understanding of the technologies and their application is limited among practitioners (Collins et al. 2016). Pretreatment genetic testing is very useful in preventing ADR in cardiovascular, cancer, HIV, and many other diseases. Patients should be encouraged for genetic testing-based treatment for cancer and other diseases, and such types of testing centers should be distributed globally. Genetic testing is far from being realized because of low specificity and sensitivity and a low incidence of an ADR or the high cost of genotyping for a disease.

13.4.1 Metabolomics and Pharmacology

Metabolomics is the study of metabolome (small molecules) present in the cells, tissues, and body fluids. Metabolic status of a person provides the close representation of the health status that is not obvious from gene expression analysis (Beger et al. 2016). The metabolic status reflects the effect of gene expression, environmental factors, diets, and the gut microbiome. For researchers in the field of clinical pharmacology, metabolomics offers a systems biology approach to understand genotype-phenotype associations, disease signatures, severity and subclass, and variability in drug response (James 2013). Clinicians measure only a small part of information contained in the metabolome to assess disease status. In the future, the narrow range of chemical analysis in medical community will be replaced by the more comprehensive metabolic signatures (Kaddurah-Daouk et al. 2015). Metabolic signatures are expected to more accurately describe specific disease and their progression and also help in differential diagnosis of disease and healthy status. The phenotypic outcome of complex interactions between genotype, diet, drug therapy, environmental exposure, and gut microflora can be investigated at the molecular level to see the overall drug response (Huang et al. 2015). Metabolic phenotyping provides an insight into disease pathophysiology and mechanisms of drug response and also predicts the risk of toxicity.

Pharmacometabolomics defines the efficacy, toxicity, or other outcomes of a drug based on a mathematical model of a preintervention metabolite signatures. Pharmacometabolomics complements genomic, transcriptomic, proteomic, and epigenomic "systems biology" approaches to drug development by taking into account the interindividual variation in drug response (Burt and Dhillon 2013). Metabolomics provides the useful prognostic indicator to complement other personalized biomarker related to genomics, transcriptomics, and proteomics because endogenous metabolites or small molecules are more closer and directly interacts with the components affecting the human health. Before utilizing biomarkers in drug development, a candidate omics-based test should be clearly defined and validated using a two-step process: (i) discovery and (ii) evaluation of clinical utility and use (Burt and Nandal 2016). Metabolomic data can be integrated with genomic results to get some novel insight into mechanisms of variation in drug response. Many scientific advances have been made to detect, identify, and quantify the large numbers of metabolites. These advances have enabled us to study hundreds or thousands of metabolites and millions of genomic variants in a single cell (Neavin et al. 2016). It is now possible to analyze the large datasets generated by omics studies to understand molecular basis of variation in disease risk and drug response.

13.4.2 CPIC and DPWG in Clinical Implementation of PGx

Dosing guideline takes into consideration patient's genotype and has been published by Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenetics Working Group (DPWG), or other organizations. One barrier to clinical implementation of pharmacogenetics is the lack of freely available, clinical practice guidelines (PharmGKB n.d.). CPIC provides guidelines that enable the translation of genetic test results for prescribing specific drugs. The guidelines are focused on genes or around drugs. CPIC guidelines are peer reviewed, published, and posted to PharmGKB with supplemental information/data and updates. CPIC's goal is to address barriers to the implementation of pharmacogenetic tests into clinical practice (CPIC n.d.). DPWG was established in 2005 by the Royal Dutch Pharmacists Association. The DPWG is multidisciplinary and includes clinical pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists, and toxicologists (PharmGKB, n.d.). The objective of the DPWG is to develop pharmacogenetic-based therapeutic (dose) recommendations and assist the prescribers and pharmacist by recommending drug prescription. DPWG has evaluated therapeutic dose recommendations for tamoxifen based on CYP2D6 genotypes (Swen et al. 2011). For PM and IM genotypes, aromatase inhibitors have been recommended for postmenopausal women due to the risk of breast cancer with tamoxifen. For IM genotypes, the recommendation is to avoid the use of a CYP2D6 inhibitor.

13.5 Therapeutic Advances in Pharmacogenomics

Progress has been achieved in the pharmacogenomics of SCAR, warfarin, and antiplatelet therapy, and a summary of developments has been represented. In recent years, many genetic polymorphisms were reported as contributing to ADR. A recent study in Japan found 1010 ADRs in 3459 adult patients, and of these, 1.6%, 4.9%, and 33% were fatal, life-threatening, and serious, respectively (Morimoto et al. 2011). The ability to predict ADR-related issues would prevent drug administration to high-risk patients. However, genetic markers were studied for several ADRs, especially for SCARs and drug-induced liver injury (DILI). As for SCARs, associations of alleles HLA-B*15:02 or HLA-A*31:01 and HLA-B*58:01 were reported for carbamazepine- and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis, respectively (Kaniwa and Saito 2013). Several HLA alleles also demonstrate drug-specific associations with DILI, such as HLA-A*33:03 for ticlopidine, HLA-B*57:01 for flucloxacillin, and HLA-DQA1*02:01 for lapatinib.

13.5.1 Warfarin Therapy

Therapeutic advances have been achieved in pharmacogenomics of warfarin. Warfarin is a commonly used oral anticoagulant for the prevention of thromboembolism in patients with deep vein thrombosis, atrial fibrillation, or prosthetic heart valve replacement (Hirsh et al. 2001). Warfarin exerts its anticoagulation effect by blocking the vitamin K regeneration cycle. Potential lethal side effects of warfarin therapy have been found, and efforts were made to reduce the ADR. Efforts were focused on developing dosing algorithms using clinical variables to predict warfarin dose (Ageno et al. 2000). However, this approach was not very efficient due to the lack of effectiveness of the programs. Warfarin maintenance was found to be associated with polymorphisms in cytochrome P450 2C9 and vitamin K epoxide reductase subunit 1. With the identifications of associated genetic factors, efforts have been made on developing dosing algorithms incorporating both clinical and genetic variables (Lee and Klein 2013).

13.5.2 Antiplatelet Therapy

Antiplatelet drugs are used in the prevention of thrombotic events associated with cardiovascular disease. The adenosine diphosphate (ADP) receptor inhibitors are a subclass of antiplatelet medications, which include clopidogrel, prasugrel, ticagrelor, and ticlopidine. Clopidogrel is one of the most commonly prescribed medications for the patients with acute coronary syndrome (ACS) and in patients undergoing percutaneous coronary intervention (PCI) (Kushner et al. 2009). Recent evidence supports a role of loss-of-function (LOF) variants in CYP2C19 as a determinant of clopidogrel response. Patients who carry LOF variants do not metabolize clopidogrel, a prodrug, into its active form resulting in decreased inhibition of platelet function and a higher risk of cardiovascular events (Perry and Shuldiner 2013). CYP2C19 LOF variants have been demonstrated to be clinically significant determinants of poor outcomes in ACS/PCI patients. With the addition of new antiplatelet therapy, the promise of translating these pharmacogenetic insights into more effective individualized antiplatelet therapy has excited the hope for future of personalized medicine.

13.5.3 Type 2 Diabetes

Genetic variants associated with incretin-based therapeutic approach for type 2 diabetes were also determined. Incretin-based therapies are used to treat patients with type 2 diabetes. Incretin effect enhancers include GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP4) inhibitors. Gliptins act by increasing endogenous

incretin levels. GLP-1 receptor (GLP-1R) and GIP receptor (GIPR) are their indirect drug targets (Tkáč and Gotthardová 2016). Several genetic variants were predicted to be involved in the physiology of incretin secretion. Only two gene variants TCF7L2 rs7903146 C>T and CTRB1/2 rs7202877 T>G minor allele carriers were associated with a smaller reduction in HbA1c after gliptin treatment (Javorský et al. 2016). HbA1c is a form of hemoglobin that is bound to glucose and indicates how well diabetes is controlled. These clinical observations could be helpful to identify patients with lower or higher response to gliptin inhibitor.

13.5.4 Cancer Therapy

Mapping of the human genome has been a boon for cancer therapy. Both somatic and germline genome provide some insight into the decision-making of cancer treatment (Hertz and McLeod 2013). The somatic genome is involved in predicting tumor behavior. Germline genome assists in determining drug exposure and toxicity. These somatic and germline informations will be very helpful in personalized therapy for cancer patients. Several new chemotherapeutic agents are available for the treatment of colorectal cancer, and it has increased the decision complexity in treatment planning. Treatment decision-making should be guided by predictive and prognostic markers. Most cytotoxic drugs induce DNA damage; the DNA damage repair pathways hold potential for yielding, predicting, and prognostic biomarkers (Kap et al. 2016). The involvement of the nucleotide excision repair pathway in the efficacy of chemotherapeutic agents should be validated for the treatment of colorectal cancer. Vincristine induces distinct death programs in primary acute lymphoblastic leukemia (ALL) cells depending on cell-cycle phase (Kothari et al. 2016). Vincristine is an important component of ALL treatment that can cause neurotoxicity. Recently, a GWAS study reported a SNP, involved in vincristine pharmacodynamics, with neurotoxicity during later phases of therapy. The strongest associations with neurotoxicity were observed for two SNPs in ABCC2, and the genotypes rs3740066 GG and rs12826 GG were associated with increased neurotoxicity (Lopez-Lopez et al. 2016). Polymorphisms in ABCC2 could be novel markers for vincristine-related neurotoxicity in pediatric ALL in early phases. These results indicate that polymorphisms in pharmacokinetic genes are associated with drug toxicity. The level of vincristine transporters or metabolizers could be used as predictors of vincristine-related neurotoxicity in ALL patients.

13.5.5 Invasive Aspergillosis

Many genetic polymorphisms have been reported that are known to alter CYP enzymes and drug receptors, drug targets, and transporters. These genetic variants can greatly influence pharmacokinetics, dose requirement and response, and

therapeutic outcomes. The clinical applications of these findings can significantly improve drug efficacy and safety. For example, invasive aspergillosis (IA) is one of the leading causes of morbidity and mortality in hematological patients (Kimura 2016). Voriconazole is used for initial therapy for IA. Individuals who carry the CYP2C19*17 gain-of-function allele were shown lower voriconazole exposure and are therefore at risk of failing IA therapy. However, there are limited data to establish a predicted relationship between voriconazole dosage and CYP2C19 metabolic capacity. A pediatric CYP2C19 rapid metabolizer (i.e., CYP2C19*1/*17) requires a voriconazole dose of 14 mg/kg twice daily (usual dose from 7 to 9 mg/kg twice daily) (Hicks et al. 2016). CYP2C19 genotype could be utilized to optimize voriconazole dose and this may be a cost-effective to improve IA therapy.

13.5.6 New Drug Labels for Clopidogrel and Warfarin

The common, complex diseases have environmental and multiple genetic influences. Therefore, drugs targeting a specific mutation can be highly successful in cancer, but we could not expect same success for chronic disease treatments. However, genes identified through GWAS and other studies provide the important protein targets. Substantial advances in the understanding of the genetic determinants of drug response have been reported, and most frequent use of pharmacogenetic data to guide drug therapy decisions can be seen in the future. Implementation of CYP2C19 genotyping for clopidogrel treatment in patients undergoing PCI is also occurring with increasing frequency, and centers Scripps Health, Vanderbilt, University of Florida, and University of North Carolina have adopted this approach (Pulley et al. 2012; Johnson et al. 2012) For instance, understanding the relationship between genetics and drug metabolism causes to issue a new drug label. In the case of a clopidogrel, new findings demonstrated that patients with genetic variants of CYP2C19 may not effectively convert the drug to its active form. After that, FDA issued a new label warning in 2010. Similarly, new labels were issued for warfarin based on genetic findings (Lesko 2008). Changes in drug labeling are likely to continue as more genetic findings are disclosed from studies on approved drugs.

13.5.7 Collaborative Efforts to Achieve the Goal of PGx

New applications and processes are needed to integrate emerging pharmacogenomic data into clinical practice. Current barriers, concerns, system limitations, and requisite infrastructure need to be addressed to achieve the true goal of pharmacogenomics. In 2010, the Pharmacy e-Health Information Technology (HIT) Collaborative was formed by nine national nonprofit organizations (Reiss and American Pharmacists Association 2011). The goal of HIT collaborative is to

ensure the pharmacist's role of providing patient care services and medication. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group has noticed that there is insufficient evidence to recommend for or against genetic testing in case of the most genetic test (Khoury et al. 2010). The challenge with such cases is that pharmacist still makes some decisions in the lack of proper evidence. In this context Veenstra and colleagues proposed a three-tiered approach, focusing on how to deal with cases with insufficient evidence for or against testing (Veenstra et al. 2010).

The ACCE (analytical validity, clinical validity, clinical utility, and associated ethical, legal, and social implications (ELSI)) model project, sponsored by the Centers for Disease Control and Prevention (CDC), has recommended the evaluation of pharmacogenomic biomarker tests (Berg 2009). Analytical validity determines how well diagnostic test measures what it is intended to measure, regardless of whether it is an expression pattern, a mutation, or a protein (Lam 2013). Clinical validity measures the ability of the test to differentiate between responders and nonresponders or to identify ADR. The clinical utility measures the ability of the test result to determine the outcome of clinical testing. Obviously, any biomarker with validation and FDA approval could enhance test implementation and utilization in the clinical settings. It is interesting to note that a large amount of PGx information has been generated, but most of the findings have not yet been applied in clinical testing and treatment. The clinical application of PGx is slow, and some physicians do not know how to interpret and apply the clinical findings in patient care (Ventola 2013).

13.6 PGx Resources

PGx discovery is based on two approaches: the candidate gene approach and GWAS. The candidate gene study focuses on genes involved in transport, drug metabolism, and targeting pathways. On the other hand, GWAS considers all genes and noncoding sequences of the human genome, assuming that all genetic elements have equal chances to affect the response of a drug. GWAS approaches came into existence after the completion of the HGP in 2000. Genome-wide studies have become more popular due to the public availability of human genomic information and low cost of sequencing.

13.6.1 PharmGKB

The Pharmacogenomics Knowledge Base (PharmGKB) is a comprehensive online resource that provides knowledge about the impact of genetic variation on drug response (Whirl-Carrillo et al. 2012). Informations retrieved from PharmGKB are very useful for clinical implementation and interpretation of clinical results. It

provides a well-known PGx association between drug and gene on the basis of dosing guidelines, drug label, clinical annotation, variant annotation, pharmacology, mechanism of action, and related pathway. It also provides the details of genes that are associated with a drug based on variant annotation, literature reviews, pathway, and information retrieved from DrugBank. PharmGKB annotates drug labels containing pharmacogenetic information approved by FDA, European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency, Japan (PMDA), and Health Canada (Santé Canada) (HCSC) and provides a brief summary of the PGx in the label (PharmGKB, n.d.). National Institute of Health (NIH)-funded scientists have studied the effect of genes on medications relevant to a wide range of conditions, including asthma, depression, cancer, and heart disease. The research findings are collected in PharmGKB.

13.6.2 PGxOne™

PGxOne™ is a proprietary clinical PGx test that provides relevant medical and clinical data and its interpretation for the treatment of patients. PGxOne™ results indicate dosing recommendations for 76 drugs. All 76 drugs are directly influenced by the 13 PGx genes (drug metabolism) covered by PGxOne™ testing. Copy number variations (CNVs) are a major source of genetic variation within an individual's genome. PGxOne™ is capable of detecting and providing information about CNVs in the CYP2D6 gene. Importantly, CYP2D6 is responsible for metabolizing approximately 25% of drugs on the market, and CYP2D6 CNVs impact the metabolism of 50% of these drugs (Ingelman-Sundberg et al. 2007). Features of PGxOne™ test (1) screens all well-established PGx genes in a single, cost-effective test; (2) detects multiple types of variations, including substitutions, insertions/deletions, and copy number variations using next-generation amplicon sequencing technology; (3) delivers results quickly via intuitive, clinically relevant, medically actionable report; and (4) provides lifetime utility of data, decreasing the need for future testing (GENEWIZ PGxOne™ n.d.).

13.6.3 Biobank

Biobank is a collection of human tissue samples or blood and medical information about donors, which are stored for long periods of time and are used for research studies. Donors voluntarily decide to give a blood or tissue sample or information about themselves for free. Imagine if every person offers and shares their health information with biobanks, then there will be a vast amount of health and clinical data, which could be used in health study for decision-making (Genetic Alliance Registry and Biobank n.d.). Biobank has the advantages of being considered in cell-, tissue-, blood-, or DNA-related studies as minimal risk research since there is no

harm to individual if their sample is examined (Biobank n.d.). Disease-related biobanks were established initially with the goal of personalized medicine. In the majority of clinical trials, the samples and blood are stored for future genetic analysis. The UK Biobank is a major health resource, with the objective of improving the health status, diagnosis, and treatment of a wide range of serious diseases – including cancer, heart diseases, stroke, diabetes, arthritis, and osteoporosis (Budimir et al. 2011). Scientist uses data from the questionnaire, physical measures, and biological samples to undertake studies to improve the health of future generations. In due course, it may be possible to find out more information about the use of the resource and follow their results.

13.7 Challenges in Implementation of PGx

13.7.1 Informed Consent and Confidentiality

Drugs that are tailored to individual genomes may require extensive genetic information of the participant in the clinical trial. Data collected from clinical trials could be stored and utilized for future research. Hence, these genetic samples could provide other information about the subject that could be unrelated to the intended study but yet might prove useful for other genetic research (Singh 2003). The patient should have high motivation to participate in the clinical trial, where the subject and patient are the same person. Therefore, the guarantee of informed consent, for all participants, is essential for the current as well as the future study. Patient, whose genetic information has been collected for clinical diagnosis, may not be interested in disclosing his/her health status and wants to keep it confidential. Sometimes, family members show their interest to know the status of inherited diseases in the patient's genetic profile. Employers or health insurers may also desire to access genetic profile of the person. Indeed, the fear of losing a job and health insurance discourage the people's interest to participate in genetic disease-related study (Nass et al. 2009). To promote the participation of patients in health and clinical study, the informations related to donor must be confidential and anonymous.

13.7.2 Technical and Educational Status

The success of PGx testing depends on the accuracy of the genomic information. The accuracy rate of hundred percent is impractical to expect in sequencing. Now, the question is how to address the sequencing errors produced. Fundamental of all sequencing method is DNA amplification. DNA amplification is well known for introducing errors and these technical errors are impossible to avoid. During the

data analysis, variation due to sequencing errors might be incorporated as a "natural" characteristic of the cell (Bavarva et al. 2015). The next challenge would be a question of how close our analyzed sequence is to the real sequence. NGS technologies and their data analysis methods must be standardized for accurate interpretation of biological problems. Auxiliary labels can be used as a tool to promote patient's awareness about PGx testing. Auxiliary labels highlight the informations related to the use and risk of drugs (Haga and Moaddeb 2015). This approach motivates the patients to consult with health provider for PGx testing. It is necessary to educate patients about PGx testing using new educational strategies. Pharmacist, physician, and other health service providers should increase and update their knowledge about PGx testing to effectively respond to patient's inquiries.

13.7.3 Economic Status, Justice, and Equity

The cost of a drug developed by PGx approach will be high due to increased research in order to identify genetic profile, develop genetic tests, and conduct clinical trials. It is also believed that few pharmaceutical companies will show their interest in developing personalized medicine due to the high cost of drug development and limited availability of market. Pharmaceutical industries show their interest in developing drugs against diseases with largest market value. An orphan population has a genotype leading to a condition for which no effective treatment is available, and pharmaceutical companies are also not attracted toward these diseases due to low market potential. Therefore, incentives must be given to pharmaceutical industries to promote drug development for rare genotypes or less common diseases (Sharma et al. 2010). One challenging issue for PGx is to develop the effective therapy for those who do not show the response to a drug (nonresponders) or difficult to treat.

There is also a disconnection between the funding agencies and the prioritization of PGx research, in terms of financial commitment, clinical trial infrastructure, and ability to adopt new strategies. Now, the question is whether national health insurance or private medical insurance companies are willing to pay the cost of drug therapy or the tests needed to prescribe them. It is also a challenge for the governments to allocate grant for drug therapy in healthcare budget. Due to high cost, PGx drugs will flow primarily into developed countries where most of the individuals can afford them. Public policy must be altered to encourage drug development via PGx, by promoting researcher, pharmaceutical companies, and market. Justice and equity are other important issues in PGx. The idea behind this is that every person should enjoy equal access to medical treatment irrespective of the virtue of race, origin, or economic status. But these inequalities in access to healthcare exist worldwide. Beyond that, it is important to address whether and how justice related to healthcare can be well served between developed and poor countries.

The most controversial issue is whether and how to integrate category of race into drug devolvement. It is discouraging that many members of the racial/ethnic community do not show their interest in participating clinical drug trials. It is noticed that a racial community receives a lower quality of healthcare than others (Nsiah-Jefferson 2003). In recent years, few drugs got approval for use by a particular racial group. Such injustice and difference are in practice because biomedical research may be biased in favor of a particular race.

13.7.4 Recommendations for Implementation of PGx

Ossorio and Duster 2005 (2005) argue that "While attempting to provide medical benefit, or market products, scientists and the pharmaceutical industry may reinvigorate the very notions of biological difference that may have resulted in racially disparate treatment and racially disparate health." Justice demands that benefits of personalized medicine must be available to individuals of all racial and socioeconomic status. The policy maker must keep in view the racial, social, or economic disparity that exists in healthcare system. Major points suggested by Peterson-Iyer (2008) for consideration in policy of PGx are (1) informed consent for the use of genetic samples, (2) improvements to subject/patient confidentiality, (3) increased post-marketing surveillance, (4) increased incentives for the development of orphan drugs, (5) revision of patent law to encourage the "rescue" of drugs, (6) subsidies to ensure that the less wealthy have fair access, (7) approval of gene-specific drugs over race-specific drugs, (8) inclusion of racial/ethnic minority groups in drug research, and (9) incentives for pharmaceutical companies to invest in and provide drug to developing countries. There are many technical, financial, and ethical hurdles in clinical implementation of PGx. In spite of these hurdles, we should start this journey with a patience and high motivation to achieve the goal.

13.8 Future Perspective

Human genome sequencing and advances in techniques that correlate specific genetic variations to diseases have played an important role in developing more effective therapy against disease. Currently, the most studied genetic variant is SNP due to low cost and high accuracy of SNP genotyping. The location and allele frequencies of genome-wide SNPs in human can be retrieved from SNP database (dbSNP) of NCBI. The future of PGx is very wide. Biotechnology industries have provided very advanced technologies for sequencing, genome annotation, expression analysis, and pharmacology. A major drawback in the study of PGx is the common occurrence of false-positive association between polymorphisms and the investigated outcome. Identification of biologically relevant polymorphism can trigger the application of PGx. Next-generation sequencing has created a plethora

of analytical and biological consideration. Scientists are very optimistic that single-cell sequencing technology will better characterize cancer and other complex diseases. The genome sequencing contributes a large amount of data but with limited insight into therapies. It has become necessary to elucidate the clinical implications of available data as well as to define the guidelines for the clinical application of PGx data. PGx knowledge is not fully utilized in clinical practice due to lack of in-depth understanding of PGx principles among the healthcare professionals. Recent PGx studies have paid attention over mitochondrial genome along with nuclear genome, because of its role in metabolism, cell cycling, cellular differentiation, and signaling. The high rate of polymorphisms in mitochondrial genome further highlights the significance of studying genetic variants in mitochondria.

There is a need to promote the field of PGx globally and aware the peoples with merits and demerits related to this field. Future advancements in PGx technologies might be able to make firm and cost-effective recommendations for drug therapy. Pharmaceutical companies are considering the importance of conducting PGx research in the early stages of drug development so that the derived knowledge could be utilized for new drug approval to avoid the risk of rejection or delayed approval. Most importantly, efforts are needed to translate the scientific outcome of PGx study into clinical practice. Patients living in urban areas are educated and aware of benefits of PGx. Efforts should be made to improve and upgrade the current status of PGx and also to implement the potential of PGx. Many PGx biomarkers corresponding to a therapeutic agent have been evaluated and more are in the process of study. These biomarkers have shown to improve the status of medication with reduced toxicity and high efficacy, which could subsequently lower the overall healthcare cost. Clinical feasibility of implementing PGx tests is dependent on medical service providers and practitioners. Patients are optimistic about the potential of PGx tests, but cost and testing time frame are barriers in the implementation of PGx.

Now, the question is the accessibility of PGx testing to common and poor people. It is surprising to know that few pharmaceutical industries are indeed in favor of the race-based medicine. FDA has approved a heart failure drug (BiDil), for its use by a self-identified racial group African-Americans, although there was no solid evidence that BiDil would be ineffective for the rest of the population. Therefore, race-based drug development practices should be discouraged to avoid racial discrimination. There are many technical- and policy-related issues associated with the wide-scale implementation of PGx. These issues must be resolved to cater the benefits of PGx equally and globally. Clinical application and cost-effectiveness cannot be the only criteria for determining the relative value of pharmacogenomics for drug therapy. Rather, it should be aimed to supplement the best practice strategies to achieve optimal drug therapy.

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