



## Pharmacogenomics: Current Application in Chemotherapy & its Future Trends

Gupta Anand\*, Chauhan Akash, Jadhav Vaishali, Jain Ashish

Shri. D.D. Vispute College of Pharmacy and Research Centre, Panvel, Maharashtra, India.

\*Corresponding author's E-mail: [akashchauhan269@gmail.com](mailto:akashchauhan269@gmail.com)

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### ABSTRACT

Pharmacogenomics focuses to predict the safety, toxicity and/or efficacy of drugs by elucidating the genetic bases for interindividual differences. Different person has different tumor responses to the same chemotherapeutic agents. These interindividual differences of drug response may be associated with age, gender, drug-drug interaction or through inherited variations in drug disposition or through gene and drug target gene. Studies in clinical pharmacology have demonstrated that most anticancer drugs are characterized by wide interindividual variability in pharmacokinetics and narrow therapeutic windows; considerable pharmacodynamics variability has also been confirmed. Systemic exposure to anticancer agents can vary up to 10-fold among patients receiving standard doses. To decrease interindividual differences in pharmacokinetics, doses of chemotherapeutic agents have traditionally been based on the surface area of patients' body. Although straightforward, this method is inadequate for many chemotherapeutic agents, since many factors can influence pharmacokinetics. Such factors can be genetic or acquired and include age, sex, and malnutrition, complex physiological changes due to concomitant disease, organ dysfunction, and tumor invasion. Among these factors, inherited differences in pharmacokinetics, especially drug metabolism, are now known to influence the efficacy and toxicity of anticancer drugs. The science of pharmacogenetics is a relatively traditional concept.

**Keywords:** Pharmacogenomics, Chemotherapeutic agents, Pharmacodynamics, Pharmacokinetics.

### INTRODUCTION

Pharmacogenomics is the science of studying the role of genome in accordance with drug response.<sup>1</sup> The name (*pharmaco+genomics*) reflects its combining of pharmacology and genomics. Pharmacogenomics scrutinize how the genetic makeup of an individual affects his/her response to drugs. It deals with the influence of acquired and inherited genetic variation on drug response in patients by correlating gene expression or single nucleotide polymorphisms with pharmacokinetics and pharmacodynamics. Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficiency with minimal adverse effects. Through the utilization of pharmacogenomics, it is hoped that pharmaceutical drug treatments can deviate from what is dubbed as the "one-dose-fits-all" approach. Pharmacogenomics also attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient's genes, the functionality of these genes, and how this may affect the efficacy of the patient's current or future treatments (and where applicable, provide an explanation for the failure of past treatments).<sup>2</sup> Such approaches promise the advent of precision medicine and even personalized medicine, in which drugs and drug combinations are optimized for narrow subsets of patients or even for each individual's unique genetic makeup. Whether used to explain a patient's response or lack thereof to a treatment, or act as a predictive tool, it hopes to achieve better treatment outcomes, greater efficacy, minimization of the occurrence of drug toxicities

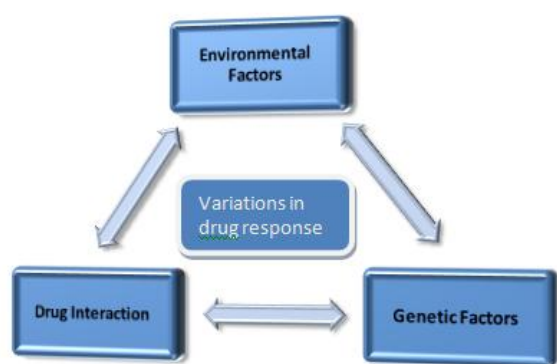
and adverse drug reactions (ADRs). For patients who have lack of therapeutic response to a treatment, alternative therapies can be prescribed that would best suit their requirements. In order to provide pharmacogenomic recommendations for a given drug, two possible types of input can be used: genotyping or exome or whole genome sequencing. Sequencing provides many more data points, including detection of mutations that prematurely terminate the synthesized protein (early stop codon).

### Pharmacogenomics in Personalized Therapy

The main aim of this is to provide individualized treatment and to predict the clinical outcome of different treatments in different patients. Around 30 years ago, the drug response was found to be altered by the genetic polymorphisms in drug metabolizing enzymes for instance, CYP450 2D6 and thiopurine-S-methyl transferases, yet more valid and predictive biomarkers for therapeutic effects and/or avoiding severe adverse effects are lacking for more than 90% of drugs which are currently in clinical practice. It is beyond doubt that pharmacogenomics promotes the development of targeted therapies, as was demonstrated earlier by US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) that the drug ivacaftor is also useful for the treatment of a subset of cystic fibrosis patients<sup>3</sup>. Ivacaftor is approved only for cystic fibrosis patients bearing the specific G551D genetic variant in the cystic fibrosis Trans membrane regulator (*CFTR*) gene, which encodes a protein that regulates chloride and water transport in the body and is defective in the



disease. Ivacaftor targets the CFTR protein, increases its activity, and consequently improves lung function. Although this and other examples (such as vemurafenib as an inhibitor of the BRAF V600E mutation in malignant melanoma suggest the demise of the blockbuster model of drug development, the concept of targeted therapy is in its early stages. One reason is that monogenic pharmacogenetic traits are mostly unable to explain the variations in a complex phenotype such as drug response. There is evidence through drug-target network analyses that most currently used drugs have multiple targets and numerous off -target effects. Genome-wide approaches such as sequencing, epigenomic profiling and metabolomics will be essential for understanding the detailed molecular architecture of disease etiology and/or drug response. Genome-wide association studies (GWAS) have implicated many new biological pathways, but this approach has limitations because most of the variants that have been associated with clinical phenotypes, such as adverse drug reactions, are not necessarily causal. There is reasonable hope that pharmacogenomic research will benefit from a combination of different omics technologies.<sup>4</sup> Recently, multi-omics studies have shown their use in discovering potential novel therapeutic targets. For instance, in one multi-omics study the integrative personal omics profile (iPOP), which combines genomic information with additional dynamic omics activities (that is, transcriptomic, proteomic, metabolomic and autoantibody profiles), from a single individual over a 14-month period demonstrated that iPOP data can be used to interpret healthy and diseased states, and can be helpful in the diagnostics, monitoring and treatment of diseased states. The major challenge, however, is the bioinformatic analysis and valid interpretation of highly complex multiomics data sets.



**Figure 1:** Multiple factors leading to variations in drug responses.

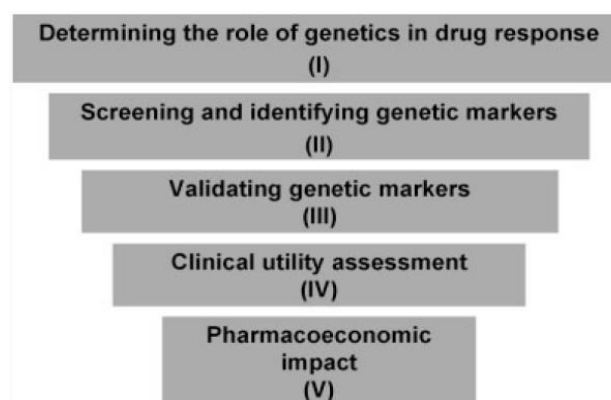
A recent National Institutes of Health White Paper by the Quantitative and Systems Pharmacology Workshop Group stated that: ‘Genomics is, in and of itself, insufficient as a means to develop and study drugs: the operation of biological networks is strongly affected not only by changes in coding sequence or gene expression but also by transient responses to external signals at the level of

protein activity, posttranslational modification, stochastic processes, etc.’ Thus, with the help of an integrative systems pharmacology approach, multiple one-dimensional biomolecular-omics data sets, as well as patient history, can be linked together to achieve a better understanding of the biology behind diseases as well as drug-response phenotypes. Such a strategy should ultimately result in the identification of novel drug targets.<sup>5</sup>

### Pharmacogenomics in Chemotherapy

Pharmacogenomics is a rapidly growing field that aims to elucidate the genetic basis for interindividual differences in drug response and to use such genetic information to predict the safety, toxicity, and/or efficacy of drugs in individual patients or groups of patients. Drug-drug interaction and environmental factors are the main contribution to a variability in drug response along with that genetic factors like drug-metabolizing enzymes, inherited variability of drug target also has significant effect on drug response and disposition. By considering the fact that the heterogeneity observed in patients for the drug response for chemotherapeutic agents, pharmacogenomics has the potential to offer individual cancer treatment regimen.<sup>6,7</sup>

Clearly, a better understanding of the genetic determinants of chemotherapeutic response will enable prospective identification of patients at risk for severe toxicity or those most likely to benefit from a particular treatment regimen. Such studies can be translated to clinical practice via molecular diagnostics (genotyping) in order to guide selection of the optimal drug combination and dosage for the individual patient. A number of detailed reviews on cancer pharmacogenomics have been published recently. This article focuses on the current and future applications of pharmacogenomics in clinical cancer therapy and cancer drug development.



**Figure 2:** Five Stages of Pharmacogenomics in Chemotherapy

### Need of Pharmacogenomics in Chemotherapy

Chemotherapeutic agents show substantial individual variability that can be explained to a great extent by genetic factors. In chemotherapeutic agents, polymorphism in genes which encodes the drug-

metabolizing enzymes, drug target and drug transporters influences the pharmacokinetics and pharmacodynamics. Several anticancer agents can cause more harm to the normal tissue than that targeted tumor or cells and their application to the body may result in tumor cell resistance, toxicity and sometimes secondary neoplasia. In order to predict a patient's predisposition to treatment complications, it is essential to consider all candidates location influencing response to the chemotherapeutic agents. This requires better understanding of metabolic pathways for activation or inactivation of these drugs, drug interactions, gender and age.<sup>8,9,10</sup>

Pharmacogenomics is an emerging field which focuses on genetic variations relevant to drug actions or response. Solid data concerning allele Variants, haplotypes and their effects on gene expression, applied to the chemotherapy regimens design and outcomes. Here are several potential polymorphic candidates' gene include the CYP isozymes, transferases, dehydrogenases, deaminases, reductases, ABC transporters,

drug receptors and DNA repair enzyme's.<sup>11</sup>

The current treatment for most cancers includes using cytotoxic chemotherapy, which is not precisely targeted to the somatic mutations that drive malignant transformation as such driver mutations are unknown for

most patients. Studies of cell line pedigrees treated with various chemotherapeutic agents have shown that some cytotoxic effects are probably heritable. Variations in the toxicities and responses experienced by cancer patients have led researchers to search for germline genetic variants associated with chemotherapy-induced phenotypes. One well-described example is that the standard dose of mercaptopurine (which is a treatment for acute lymphoblastic leukaemia (ALL)) results in life-threatening toxicity for individuals with certain variant alleles of thiopurine S methyltransferase (TPMT). The US Food and Drug Administration (FDA) now recommend genotyping of TPMT, and individuals with inactive alleles are often successfully treated with reduced doses of mercaptopurine<sup>4</sup>. Additional key germline genetic variants that are associated with cancer-drug-induced phenotypes are shown in Table 1.<sup>12</sup>

The table shows key germline genetic variants associated with cancer drug-induced phenotypes with replication in multiple cohorts and strong functional evidence. *CYP2D6*, CYP2D6 cytochrome P450, family 2, subfamily D polypeptide; FDA, US Food and Drug Administration; GWAS, genome-wide association study; *SLCO1B1*, solute carrier organic anion transporter family, member 1B1; *TMPT*, thiopurine S-methyltransferase; *UGT1A1*, UDP glucuronosyltransferase 1 family, polypeptide A1.

**Table 1:** Examples of Germline genetic variants associated with cancer-drug-induced phenotypes.

Drug	Mechanism of action	Cancer type (or types)	Genes	Variants	Phenotype	Type of study	Evidence
Mercaptopurine	Antimetabolite that inhibits purine nucleotide synthesis (involved in DNA replication)	Paediatric acute lymphoblastic leukaemia	TPMT	rs1142345 rs1800460 rs1800462 rs1800584	Myelosuppression	Candidate gene	FDA label recommends genotyping
Irinotecan	Inhibits topoisomerase I (involved in DNA replication and transcription)	Colorectal, lung	UGT1A1	rs8175347	Neutropoenia, diarrhoea	Candidate gene	FDA label recommends genotyping
Tamoxifen	Inhibits the oestrogen receptor	Hormone-receptor-positive breast	CYP2D6	rs16947 rs1065852 rs28371706 rs28371725 rs35742686 rs3892097 rs5030655 rs5030656 rs59421388 rs61736512	Tamoxifen metabolism, progression-free and overall survival	Candidate gene	Conflicting results may be due to study design and quality control; studies are ongoing
Methotrexate	Antimetabolite that inhibits folic acid metabolism (involved in DNA replication)	Paediatric acute lymphoblastic leukaemia	SLCO1B1	rs11045879	Methotrexate clearance, gastrointestinal toxicity	GWAS	Association was genome-wide-significant; replicated in multiple cohorts; <i>in vitro</i> functional evidence

### Study Design for Cancer Pharmacogenomics

The candidate gene approach has often been used in cancer pharmacogenomics<sup>6</sup>; variants in known drug-metabolizing enzymes and drug targets are tested for association with phenotypes of interest. Genotyping arrays containing hundreds of SNPs in known drug absorption, distribution, metabolism and elimination (ADME) genes - such as the Affymetrix DMET chip and the Illumina VeraCode ADME Core Panel-can be useful in pharmacogenomic candidate gene studies. Of course, the candidate gene approach requires a priori biological knowledge and will miss unknown regions of association, but the candidate gene approach may still have merit in cancer pharmacogenomics when patient sample sizes are limited, particularly if pharmacokinetic data are also available. However, as genotyping and sequencing costs continue to decline, every effort should be made to carry out comprehensive genome-wide analyses to make the best use of available patient samples.<sup>13,14</sup> Clinical trials offer the ideal infrastructure for pharmacogenomic studies because of their consistent drug dosing and phenotype collection. Phase I trials are designed to determine the maximum tolerable dose of a new drug, and Phase II trials estimate the effectiveness of the drug to determine whether it should proceed to Phase III. The sample sizes of Phase I and II trials in oncology are often less than 100 individuals and thus are seldom amenable to genome-wide pharmacogenomic discovery studies, but they may be useful in candidate gene studies. Comparative Phase III trials often involve hundreds to thousands of patients and are thus useful sources of data for genome-wide association studies (GWASs). Prospective cancer pharmacogenomic studies can also be designed separately from clinical trials, but care should be taken to ensure that consistent dosing regimens and phenotype and covariate collection procedures are followed. Retrospective studies are possible and may allow a larger sample size, but inconsistent treatments and data collection may confound results.<sup>15,16</sup>

### Genetic Polymorphism of Drug Targets

Genetic variation in drug targets (e.g., receptors) can have a profound effect on drug efficacy, with over 25 examples already identified (Table 1). Sequence variants with a direct effect on response occur in the gene for the  $\beta$ 2-adrenoreceptor, affecting the response to  $\beta$ 2-agonists, arachidonate 5-lipoxygenase (ALOX5), affecting the response to ALOX5 inhibitors and angiotensin-converting enzyme (ACE), affecting the renoprotective actions of ACE inhibitors. Genetic differences may also have indirect effects on drug response that are unrelated to drug metabolism or transport, such as methylation of the methylguanine methyltransferase (MGMT) gene promoter, which alters the response of gliomas to treatment with carmustine. The mechanism of this effect is related to a decrease in the efficiency of repair of alkylated DNA in patients with methylated MGMT. It is critical to distinguish this target mechanism from genetic

polymorphisms in drug-metabolizing enzymes that affect response by altering drug concentrations, such as the thiopurine methyltransferase polymorphism associated with the hematopoietic toxicity of mercaptopurine and susceptibility to radiation-induced brain tumors. The  $\beta$ 2-adrenoreceptor (coded by the *ADRB2* gene) illustrates another link between genetic polymorphisms in drug targets and clinical responses. Genetic polymorphism of the  $\beta$ 2-adrenoreceptor can alter the process of signal transduction by these receptors. Three single-nucleotide polymorphisms in *ADRB2* have been associated with altered expression, down-regulation, or coupling of the receptor in response to  $\beta$ 2-adrenoreceptor agonists.<sup>17,18,19</sup>

Single-nucleotide polymorphisms resulting in an Arg-to-Gly amino acid change at codon 16 and a Gln-to-Glu change at codon 27 are relatively common, with allele frequencies of 0.4 to 0.6, and are under intensive investigation for their clinical relevance. A recent study of agonist-mediated vasodilatation and desensitization revealed that patients who were homozygous for Arg at *ADRB2* codon 16 had nearly complete desensitization after continuous infusion of isoproterenol, with venodilatation decreasing from 44 percent at base line to 8 percent after 90 minutes of infusion (Fig. 4). In contrast, patients homozygous for Gly at codon 16 had no significant change in venodilatation, regardless of their codon 27 status. Polymorphism at codon 27 was also of functional relevance; subjects homozygous for the Glu allele had higher maximal venodilatation in response to isoproterenol than those with the codon 27 Gln genotype, regardless of their codon 16 status (Fig. 4). These results are generally consistent with those of studies showing that the forced expiratory volume.

In one second (FEV1) after a single oral dose of albuterol was higher by a factor of 6.5 in patients with the Arg/Arg genotype at codon 16 of *ADRB2* than in those with the Gly/Gly genotype (Fig. 4). However, the influence of this genotype was different in patients receiving long-term, regularly scheduled therapy with inhaled  $\beta$ -agonists. Among these patients, those with the Arg/Arg genotype had a gradual decline in the morning peak expiratory flow measured before they had used medication, whereas no change was observed in patients with the Gly/Gly genotype. In addition, the morning peak.

Expiratory flow deteriorated dramatically after the cessation of therapy in patients with the Arg/Arg genotype, but not in those with the Gly/Gly genotype. These data suggest that a codon 16 Arg/Arg genotype may identify patients at risk for deleterious or nonbeneficial effects of regularly scheduled therapy with inhaled  $\beta$ -agonists; the data also suggest that these patients may be candidates for alternative schedules of therapy, earlier initiation of anti-inflammatory agents, or both. These findings are also consistent with the aforementioned desensitization of the  $\beta$ 2-adrenoreceptor in patients with a codon 16 Arg/Arg genotype. At least 13



distinct single-nucleotide polymorphisms have been identified in *ADRB2*. This finding has led to evaluation of the importance of haplotype structure as compared with individual single nucleotide polymorphisms in determining receptor function and pharmacologic response. Among 77 white, black, Asian, and Hispanic subjects, only 12 distinct haplotypes of the 8192 possible *ADRB2* haplotypes were actually observed. The bronchodilator response to inhaled  $\beta$ -agonist therapy in patients with asthma revealed a stronger association between bronchodilator response and haplotype than between bronchodilator response and any single nucleotide polymorphism alone. This is not surprising, because haplotype structure is often a better predictor of phenotypic consequences than are individual polymorphisms. This result suggests that it would be desirable to develop simple but robust molecular methods to determine the haplotype structure of patient.<sup>20,21,22</sup>

### Current Success in Pharmacogenomic

- 1. Codeine:** Codeine (3-methyl morphine) in children and adults is one of the most widely used drugs for the treatment of mild to moderate pain. Codeine itself does not have its analgesic effect, it gets converted to its pharmacologically active metabolite, morphine in liver which is responsible for analgesic activity and have approximately 600 times more analgesic effect than that of codeine. Recently the use of codeine has been decreased due to codeine related toxicity. The serious or fatal adverse reaction have been observed in the neonate after receiving the breast milk of the mother receiving standard dose of codeine for post-partum pain. Tonsillectomies and adenoidectomies adverse effect have been reported in the children taking codeine for relieving pain. The cytochrome P450 2D6 (CYP450 2D6) is the enzyme which is responsible for the biotransformation of the codeine to morphine, is highly polymorphic with over 100 genetic variants described in the CYP450 2D6 gene. The patient with more than three or more functional copies of CYP450 2D6 are classified as ultra-rapidly metabolizers, which rapidly convert codeine to morphine and produces morphine toxicity even at very low dose.<sup>(28,33)</sup> The morphin toxicity observed are respiratory depression and in rare case the death have been reported due to presence of these highly active alleles (CYP4502D6\* 1xN/\*2xN/\*17Xn/\*35Xn; where N represent number of copies). In some patient the codeine does not get converted into morphine due to the presence of poor metabolizing enzyme CYP4502D6, hence minimal analgesic effect and pain relief.<sup>21, 22,23</sup>

The amount of morphine produced from the codeine varies from individual ranging from 0% to 75%. Clinical practice guideline has recently been developed to inform physician on the use of genetic
- 2. Warfarin:** Warfarin is an anticoagulant used for prevention and treatment of venous thromboembolism by inhibiting the enzyme vitamin K epoxide reductase, encoded in *VKORC1*, due to which the amount of vitamin K available for synthesis of coagulation factor get decreased. The dose of warfarin required to produce anticoagulant effect varies about 20 fold from individual to individual patient. In case of warfarin several adverse effects can be observed such as bleeding or thrombosis due to narrow therapeutic window and inappropriate dosing in individual. The dose the warfarin depends upon both the genetic and clinical factor. For example, genetic variant in *VKORC1* as well as the cytochrome P450 2C9 (CYP2C9) gene, which is primarily responsible for metabolizing the pharmacologically active S-warfarin isomer, confer an increased variant [*VKORC1*rs9923231, CYP2C9 rs1799853(\*2), rs1057910] requires lower warfarin doses to achieves equivalent therapeutic effects. The several other genes that influences the warfarin dose are cytochrome P450 4F2 (CYP4F2) and gamma glutamyl carboxylase (GGCX). The impact of the genes on the variation of warfarin dose is very minor after the accounting for *VKORC1* and CYP2C9 variant. The recent study shows a significant association between warfarin and *VKORC1*/CYP2C9 genome in pediatric patient, which shows that same genetic variants are important for warfarin dosing in children. For the predication of the accurate dose of warfarin several pharmacogenetic based dosing algorithms have been developed.<sup>24,25</sup>
- 3. Carbamazepine:** Carbamazepine is one of frequently used anticonvulsant drug used for treatment of the epilepsy, trigeminal neuralgia, bipolar disorder and seizure disorder in both children and adult. The several sever side effect have been observed in patient taking carbamazepine such as life-threatening cutaneous adverse reaction, Hypersensitivity reaction, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Hypersensitivity reaction is generally characterized by high fever, skin eruption and involvement of at least one internal internal organ with approximately mortality of 10%. SJS and TEN are serious blistering reaction of skin and mucous membrane which mortality rate range from 10% to 50% 53. The genetic variants in human leukocyte antigen (HLA) region lead to carbamazepine induced hypersensitivity reaction in both child and adult. The higher risk of SJS/TEN have been reported in patient carrying the HLA-B\*1502 variant. While HLA-A\*31:01 allele is primarily predictive for HSS. The carbamazepine- induced SJS/TEN largely depend on the genetic of the patient ancestry. The number of the HLA-B\*1502 variant is high (10-15%) in the Asia



including china, Malaysia, Thailand, Indonesia, Tawani and Vietnam but rare (<1%) in Japan, Korea, Africa, America, European, and Hispanic population.<sup>26,28</sup>

Recently it have been reported that in European population the carbamazepine-induced adverse reaction including SJS/TEN and HSS is due to HLA-A\*31:01 Haplotype. Pharmacogenomic testing for HLA-B\*15:02 is in standard practice in at least 50 hospitals in Taiwan and is currently recommended by the FDA for patient with ancestry in at risk-populations. For clinicians, clinical practice guidelines are available to make genotype- based decision for patient with an indication with carbamazepine therapy.

### Pharmacogenomics and Drugs Development

Initially the drug discovery in psychiatric was based on the serendipity. After the identification of the lithium in 1949 and chlorpromazine in 1950s, the purgative mechanism of action was elucidated after drug were shown to be efficacious. The newer drug discover paradigms depends on the synthesis and identification of novel compound through combinatorial chemistry and screening for biological screening for biological activity against known receptor or other biological targets with established endogenous ligands or substance.<sup>27,30</sup> The experimental paradigms used in the pharmacogenomics were borrowed from the field of the population genetics and methodology used in earlier genetic study of common complex disease. According to the human genome project all the human genes available act as the potential drug target. Then the main challenge of the drug discovery is the functional and therapeutic utilization of these genes and their expressed product. The pharmacogenomics brought the Experimental paradigms from the field of population genetics and the methodology used in earlier genetic studies of common diseases.

DNA microarray is an emerging powerful technological breakthrough that enables the study of global gene expression pattern and sequence variation at genome level. DNA micro assay is the extended form of the southern blot procedure in which the stretching of different cDNAs or oligonucleotide are carried on a solid surface such as silica or glass plate. In microarray each DNA species represent specific gene or expressed sequence tag, which is used to identify different SNPs or transcripts by hybridization and fluorescence detection.<sup>31,32</sup>

### CONCLUSION

Pharmacogenomics is one of the most important tool used worldwide to find the adverse drug reaction as well as for the development of new drug. The cost and time for the development of new drugs can be minimized with the help of this tool. The personalization of the treatment can be carried out with the help of

Pharmacogenomic/pharmacogenetic study. So, the Pharmacogenomics is the future of the drug discovery and development. At present, however, it is not clear whether and what extent the genomic hypothesis can be tested within the framework of available clinical trial methodology. For example, the sample size for phase clinical trial is not more than 3000 to 4000 patient. But the genomic studies reduce the sample size than that of the current resource of any single pharmaceutical company or an academic laboratory.

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