INTRODUCTION
Pharmacogenomics is a science of determining how genetic variability influences physiological responses to drugs, from absorption and metabolism to pharmacologic action and therapeutic effects. Pharmacogenomics refers to the application of genome-wide approaches in order to understand genetic influence on drug response and to develop novel drugs. This application of pharmacogenomics has implications in predicting a patient’s response to medications, reducing adverse events and improving rationality of drug development. Pharmacogenomics profoundly change the way clinical drug trials are conducted, as well as influencing drug development process. This review provides an overview of the pharmacogenomics application on drug discovery and development.

Key words: Pharmacogenomics, drug, discovery, development

ABSTRACT
Individual variations in the response to drugs and drug toxicity occur commonly in the clinical setting and in drug development research protocols. Cumulative evidence strongly suggests that genetic polymorphisms in drug metabolizing enzymes, transporters, receptors and other drug targets are contributing to inter-individual differences in the efficacy and toxicity of drugs. Pharmacogenomics refers to the application of genome-wide approaches in order to understand genetic influence on drug response and to develop novel drugs. This application of pharmacogenomics has implications in predicting a patient’s response to medications, reducing adverse events and improving rationality of drug development. Pharmacogenomics profoundly change the way clinical drug trials are conducted, as well as influencing drug development process. This review provides an overview of the pharmacogenomics application on drug discovery and development.

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INTRODUCTION
Pharmacogenomics is a science of determining how genetic variability influences physiological responses to drugs, from absorption and metabolism to pharmacologic action and therapeutic effects. Pharmacogenomics refers to the application of genome-wide approaches in order to understand genetic influences on drug response and to developing novel drugs. Historically, pharmacogenetics studies were developed initially to understand individual differences in drug pharmacokinetics and metabolism, and were often focused on single gene polymorphisms (SNPs), especially in drug metabolism genes.

Although ‘pharmacogenomics’ and the older term ‘pharmacogenetics’ are often used interchangeably, pharmacogenomics is broader in scope, and refers to the complex interactions of genes across the genome. Pharmacogenomics includes identifying candidate genes and polymorphisms, correlating these polymorphisms with possible therapies, predicting drug response and clinical outcomes, reducing adverse events and selecting dosing of therapeutic drugs on the basis of genotype.

In the 21st century, emerging genome science and technologies are shifting the paradigm of drug discovery research and the development process, and are improving the strategies of medical care. The Human Genome and International HapMap project has opened the chance for new generation of diagnostics tools aimed at identifying and characterizing human diversity. In particular, they have provided a large resources of SNPs that explain much of variation between different individuals and different ethnic groups. The differences in response to medications are often greater amongst members of a population than they are within the same person or between monozygotic twins. The existence of large population differences with...
The source of individual variation in response to drugs may be SNPs or mutations. SNPs are abundant in the human genome and may affect the pharmacokinetics and pharmacodynamics of a drug. Cumulative evidence strongly suggests that genetics polymorphisms in drug metabolizing enzymes, transporters, receptors and other drug targets are contributing to interindividual differences in the efficacy and toxicity of drugs. Individuals respond differently to drugs and sometimes the effects are unpredictable. The use of pharmacogenomics is to identify genetic polymorphisms that predispose patients to adverse drug effects, although they may occur in only a small subset of the people treated with a new drug. Given the potential value of knowing all the possible factors that influence the effects of new agents, it is likely that pharmacogenomics will have an increasingly important role in drug discovery and development. This paper is addressing the pharmacogenomics and its application in the process of drug discovery and development.

**DISCUSSION**

The process of drug development includes pathway identification and target selection, screening of chemical compounds, drug development, preclinical and clinical studies, and also drug marketing. The promise of pharmacogenomics is that it will solve two major problems in healthcare, the diminishing productivity of the drug development process and the unacceptably high proportion of patients who receive either no benefits from drugs or experience adverse events. Its proponents suggest that pharmacogenomics will be part of a fundamental transformation in the drug discovery and development process, while current clinical trials are designed to observe effects in populations rather than to give information on interindividual variation in drug response.

The two most important concerns for new drug development are efficacy and safety. Before the advent of pharmacogenetic tools, the predictability of both these factors was very low. This will be translated into heavy financial loss due to attrition of the drug compound during clinical trials. In current times, the scenario has changed and with the availability of sophisticated pharmacogenetic tools, the attrition rate can be significantly reduced. This will be translated into reduction in loss of financial resources for drug development. With in vitro methods, it can be identified during preclinical studies, whether the drug is metabolized by polymorphic enzymes, and a decision regarding continuation of the trial can be made. This information can also help in selecting appropriate patients with normal metabolizing enzymes in phase I clinical trial, it can also help prevent adverse events.

The implementation of pharmacogenomics in efficacy and safety studies has impacted a broad spectrum of drug discovery and development activities. Figure 1 shows a framework for the application of the pharmacogenomics process at various stages throughout drug discovery including target and candidate selection, clinical development, drug approval and life cycle management (LCM).

1. **Pharmacogenomics and Drug Target Selection**

The process of drug discovery starts with the identification of a potential target at which the drug can act. The target can be an enzyme in a vital pathway, a receptor, a transporter, a protein in signal transduction or any protein produced in a pathological condition. After sequencing of the human genome, the number of drug target was estimated to be around 8000 and 4990 out of which could number of drug target was estimated to be around 8000 and 4990 out of which could have variations owing to genetic polymorphisms, and drugs which are based on targets showing wide polymorphisms can have variations in their effect. This can lead to inconsistent results in the preclinical and clinical studies. Thus, the targets can be characterised based on pharmacogenetic studies and suitable drug compounds selected for further investment at an early stage.

In most cases, variation in drug response in a disease is attributed to many genes rather than a single gene mutation. In such cases, it would be appropriate to do a pharmacogenomic study comparing SNPs maps and gene expression between normal and affected individuals to identify the genetic factors associated with the disease, and thus provide newer targets of drug development. Potential future drug targets can be called as "tractable" or "drugable" targets. Novel approaches for high throughout experiments to discern associations between disease and disease traits with large numbers of tractable...
These comprise the first exposure of humans to a putative medicine, focused on safety. Use results from Phase I and II trials to design an optimal large-scale Phase III study. Conducted in patients and look to establish an initial indication that the compound is effective. Genotyping might be carried out to try and identify and correlate polymorphisms with phenotypic elements. Studies to assess the following:

- Genotyping might be used for genotype–phenotype correlations
- Genotyping could be used to attempt to associate specific polymorphisms with differences in efficacy using the candidate-gene approach
- Certain research subjects with particular genotypes might be enrolled preferentially
- Large-scale, long-term post-marketing studies
- Focused on identifying morbidity, mortality and adverse events
- Might identify new indications

Table 1 Phases of clinical development

<table>
<thead>
<tr>
<th>Phase</th>
<th>Studies</th>
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<tbody>
<tr>
<td>I</td>
<td>These comprise the first exposure of humans to a putative medicine, focused on safety. Up to 100 individuals may take part in a series of studies. Designed to provide information about pharmacokinetics and pharmacodynamics. Not always randomized. Useful in identifying minimal and maximal dosages.</td>
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<tr>
<td>II</td>
<td>Conducted in patients and look to establish an initial indication that the compound is effective. Involves up to 1000 individuals. Focus on drug efficacy, safety and determining appropriate range of drug doses in patients with a disease or condition of interest. Can be randomized.</td>
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<td>III</td>
<td>These large trials, costing tens or even hundreds of millions of pounds, provide the most convincing evidence of efficacy and safety. Must involve a comparison of new therapeutic intervention with standard treatment or placebo. Generally a randomized and blinded study. Often the final stage of testing before new drug approval can be granted.</td>
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<tr>
<td>IV</td>
<td>Phase IV studies</td>
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Table 2 Genotyping at different stages of clinical trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Genotyping might be carried out to try and identify and correlate polymorphisms with phenotypic elements (such as pharmacokinetic/pharmacodynamic properties, excretion and serum levels). Certain research subjects with particular genotypes might be excluded from the trial. Certain research subjects with particular genotypes might be enrolled preferentially.</td>
</tr>
<tr>
<td>II</td>
<td>Genotyping might be used for genotype–phenotype correlations. Genotyping could be used to attempt to associate specific polymorphisms with differences in efficacy using the candidate-gene approach.</td>
</tr>
<tr>
<td>III</td>
<td>Use results from Phase I and II trials to design an optimal large-scale Phase II study. Test candidate genes for efficacy and metabolism. Might be useful to conduct large-scale genotyping to discover new pharmacogenomic markers. Identify which sub-populations show more adverse events to certain drugs. Identify responders versus non-responders to certain drugs.</td>
</tr>
<tr>
<td>IV</td>
<td>Studies to assess the following: rare adverse events and the relationship of such events to specific sub-populations. Marketing considerations; that is, whether a diagnostic test might be capable of distinguishing the drug of interest from competitors, and whether the market for a given drug would justify the development of diagnostic testing.</td>
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Table 2 depicts some possibilities for incorporating genotyping into different phases of a clinical trial. At present, in most of the trials reported in the literature, pharmacogenomic profiling is applied prospectively mainly during Phase I trials. Research subjects are enrolled into the trial on the basis of genotypes that predict metabolic capacity to respond to the drugs of interest, or genotypes that could prevent adverse events through particular pathways. At the Phase II level, the candidate-gene approach can be used in conjunction with genotyping to correlate particular polymorphisms with phenotypic differences in efficacy. In later Phase III trials, pharmacogenomic profiling can be used to distinguish responders from non-responders.

3. Pharmacogenomics for Predicting Efficacy and Safety of Drug

In addition to its direct clinical impact on patients and healthcare systems, variable efficacy is also an important issue for drug development. Failure to show efficacy in phase II studies is the most common reason for terminating the development of medicines. In contrast to the conventional methods where preclinical and clinical studies are done with the purpose of determining efficacy, drugs which have designed with pharmacogenomic support have a predetermined efficacy status. The chance of a drug failing in preclinical and clinical studies due to the absence of efficacy is minimized. The efficacy of a drug, is determined by appropriate target selection, which can be guided by pharmacogenomic methods. For some drugs, measurement of expression of an obvious molecular drug target will provide a reasonably accurate basis for pharmacogenomic selection of patients. For example, the drug Herceptin (trastuzumab), an anti-HER2 monoclonal antibody against metastatic breast cancer, was found to be effective only in women who were over expressing the HER2 protein during early clinical trials. In the subsequent trials, studies were done only on women found to be over expressing the HER2 protein. The availability of a test for a subgroup with a higher probability of positive response to treatment with Herceptin allowed this drug to progress through further studies to approval.
A major challenge in pharmacogenomics application for predicting efficacy is that the efficacy phenotype is likely to be multigenic and potentially confounded by environmental factors, thus require more research to be fully clinically applicable. Nonetheless, prediction for efficacy is a hugely promising area for pharmacogenomics. By using genetic and other biomarkers to identify appropriately responding subgroups in phase II studies, compounds that are effective in patient subgroups may be developed further, significantly speeding the delivery of new medicines to meet patient needs and increasing the productivity of pharmaceutical research and development.14

The second major concern in a clinical trial is drug safety profile. During a clinical trial, the occurrence of a serious adverse drug reactions (ADRs) could jeopardize the drug status. Usually, such an event would culminate in the termination of the trial. There are two important places in the development pipeline where pharmacogenomics studies can contribute toward safety. The first occurs during early clinical trials in which indication of adverse events (AEs) can present considerable risk to a development program; however this risk can be effectively manage during clinical trials to allow decisions to be made in timely manner, cutting the lag time between steps in the progression of a drug through the pipeline. The overall safety of medicine in the clinical trials would increase considerably, and abrupt and abandonment of drugs at later stages of development could be avoided.15 The second application of pharmacogenomics on drug safety is expected in phase IV when AEs to be observed only after tens of thousands of patient have had exposure to the drug. This is the most critical time for new safety concerns to arise and high cost-burden for drug developer if serious adverse events lead to a product withdrawal. This implies to an improved post marketing surveillance system in which DNA from AEs patient is available, enabling rapid clarification of a diagnostic profile or test of extremely high sensitivity and high specificity.6

Drug toxicity occurs mainly due to increased plasma drug levels, which may be the result of poor metabolizing capacity owing to genetic polymorphisms.6 The metabolizer phenotype describes the patient’s ability to metabolize certain drugs and is based on the number and type of functional alleles of certain genes that a patient carries. These genes most commonly encode the CYP enzymes. The metabolizer phenotype can range from “poor,” used to describe patients with little or no functional activity of a selected CYP enzyme, to “ultra-rapid,” used to describe patients with substantially increased activity of a selected CYP enzyme. Poor metabolizers are unable to metabolize certain drugs efficiently, resulting in potentially toxic build-up of an active drug or the lack of conversion of a prodrug into an active metabolite. In contrast, in ultra-rapid metabolizers, an active drug is inactivated quickly, leading to a subtherapeutic response, while a prodrug is quickly metabolized, leading to rapid onset of therapeutic effect. Table 3 summarizes the effects of CYP variation on therapeutic efficacy.22

<table>
<thead>
<tr>
<th>Metabolizer phenotype</th>
<th>Active drug (inactivated by metabolism)</th>
<th>Prodrug (needs metabolism to produce active metabolite)</th>
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<tbody>
<tr>
<td>Poor</td>
<td>Increased efficacy, active metabolite may accumulate, usually require lower dose to avoid toxic accumulation</td>
<td>Decreased efficacy, prodrug may accumulate, may require lower dose to avoid toxic accumulation, or may require alternate drug</td>
</tr>
<tr>
<td>Ultra-rapid</td>
<td>Decreased efficacy, active metabolite rapidly inactivated, usually require higher dose to offset inactivation</td>
<td>Increased efficacy, rapid onset of effect, may require lower dose to prevent excessive accumulation of active metabolite</td>
</tr>
</tbody>
</table>

4. The Promise of Pharmacogenomics in drug discovery and development

The promise of pharmacogenomics is that it will solve two major problems in healthcare: the diminishing productivity of the drug development process and the unacceptably high proportion of patients who receive either no benefits from drugs or experience adverse events. Pharmacogenomics not only can provide insights into safety signals that may become apparent at phase II but also underscore the role of pharmacogenomics in providing information to help research and development decision making. This use of pharmacogenomics data will be critical in facilitating the rational development of new medicine.14

The ultimate promise of pharmacogenomics is the possibility that knowledge of a patient’s DNA sequence might be used to enhance drug therapy to maximize efficacy, to target drugs only for patients that are likely to respond and to avoid adverse drug reactions.23 It would expected when the technology is fully mature and pharmacogenomics was integrated into drug development processes and incorporated into clinical practice:

- The rate of delivery a new medicines through pharmaceutical research and development will increase, utilizing a greater understanding of safety issues and defining genetically-defined patient groups in which a compound is effective.
- Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This accuracy not only will maximize therapeutic effects but also decrease damage to nearby healthy cells.14,24
- Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug.
- Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved and a wider range of possible drug targets will promote a net decrease in the cost of healthcare.14,24

CONCLUSION

The variations in drug response can be better studied with wider application of pharmacogenomic methods. This integrated approach will enhance our comprehension on how drug metabolism genes are regulated and how this knowledge can be better applied to provide value-added data in drug discovery and development process. The potential for widespread use of pharmacogenomics in the drug development process merits an examination of its fundamental impact on clinical-trial design and practice. This application of pharmacogenomics has implications for predicting a patient’s response to drugs, reducing adverse events and improving rational drug development.
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