

## Current update of pharmacogenomic role in drug discovery and development: a narrative review

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### ABSTRACT

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Pharmacogenomics currently has an essential role in drug discovery and development. Study related to pharmacogenomics has increased rapidly since the human genome project was completed in the early 20<sup>th</sup> century. It increased awareness of the importance of personalized medicine, which is expected to be safer and more beneficial for human health. This article aimed to review recent developments regarding pharmacogenomics in drug discovery and development. In addition, the challenges in the implementation of pharmacogenomics in drug development and clinical practice were also discussed. Hopefully, these challenges can be overcome through collaboration between researchers, practitioners, and the government therefore precision and personalized therapy can be applied in clinical setting.

### ABSTRAK

Farmakogenomik saat ini memiliki peranan penting dalam penemuan dan pengembangan obat. Penelitian terkait farmakogenomik meningkat pesat sejak proyek genome manusia selesai pada sekitar awal abad ke-20. Hal ini telah meningkatkan kesadaran akan pentingnya pengobatan secara individual yang diharapkan lebih aman dan bermanfaat untuk mengatasi masalah kesehatan manusia. Artikel ini bertujuan untuk mengulas kembali perkembangan terkini terkait peranan farmakogenomik dalam penemuan dan pengembangan obat. Selain itu, tantangan dalam implementasi farmakogenomik dalam pengembangan obat dan praktek klinik juga dibahas. Diharapkan, tantangan tersebut dapat diatasi melalui kerjasama antara peneliti, praktisi dan pemerintah sehingga pengobatan secara individu dan presis dapat diimplementasikan dalam klinik.

### INTRODUCTION

Since the human genome project was completed in early 21<sup>st</sup> century, genomic research in health science and medicine has developed rapidly. One of the studies in genomic is pharmacogenomic. In this field, structural and functional genomics are investigated to reveal their effect on drug responses.<sup>1,2</sup> Pharmacogenomic approach is also used to implement precision and personalized medicine, which suggests more safe and beneficial for human health.<sup>3</sup>

Drug discovery and development

are long and expensive research in science and medicine.<sup>4</sup> In the post-genomic era, this process might be not shortened significantly, but it could be more productive. Computational-based bioinformatics bridge the human genomic database and drug compound analysis therefore drug screening process becomes more focused, effective and efficient. Moreover, the utilization of genomic data to ensure effectivity and drug safety or repurposing the common-use drug for other conditions has made the drug development process more precise and functional.<sup>5</sup>

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Pharmacogenomics also plays a role in adjusting drug doses in the clinical setting. Some drugs commonly used in clinical practice have been prescribed based on the pharmacogenomic guideline, such as analgesic, anticoagulant, antiplatelet, and antiepileptic.<sup>6</sup> Genomic information has also been considered in a clinical trial, such as participant

selection and dose stratification.<sup>7</sup> This paper aimed to update knowledge about pharmacogenomics in drug discovery and development (FIGURE 1). The challenge in implementing pharmacogenomics from translational to clinical settings was also explained at the end of this review.

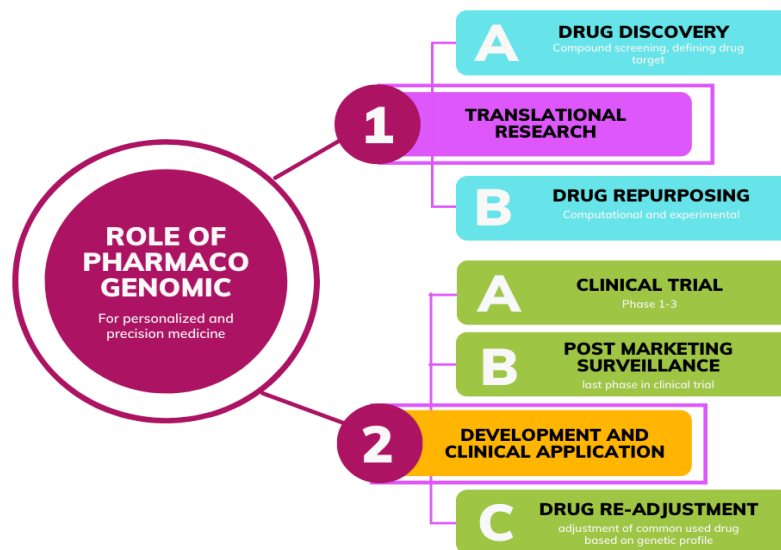


FIGURE 1. Outline topic. This paper reviewed about role of pharmacogenomic in drug discovery and development for personalized and precision medicine in the future.

## MATERIAL AND METHODS

We used the PUBMED database for searching reference articles. We used queries “pharmacogenomic AND drug discovery AND drug development”, “pharmacogenomic AND drug discovery”, “pharmacogenomic AND precision medicine”, “pharmacogenomic AND drug repurposing” and “pharmacogenomic AND drug development”. All types of open access articles related to this topic were included in this review.

## DISCUSSION

### Drug discovery

We have entered a new phase of the genomics era where it is possible

to comprehensively characterize the genomes of patients and healthy individuals. This era has brought to precision medicine with a genomic approach to identify gene variations that directly lead to new targets for treating common conditions.<sup>8</sup> One of the fields of pharmacogenomics has been developed into genome-related studies to identify new variants associated with phenotypes to drug response. Although these effects have been largely ignored to the present, with the increase in the clinical use of pharmacogenomics, they are rapidly getting attention. The potential of genome analysis in drug development can be studied using genome-wide association (GWAS), linkage analysis, exome sequencing, and whole-genome

sequencing.<sup>9</sup> Over the past two decades, the drug discovery process has evolved from animal-based testing models with low throughput to molecular target-based with high throughput.<sup>10</sup> The

drug discovery process involves target identification, target validation, lead identification, and lead optimization (FIGURE 2).<sup>11</sup>

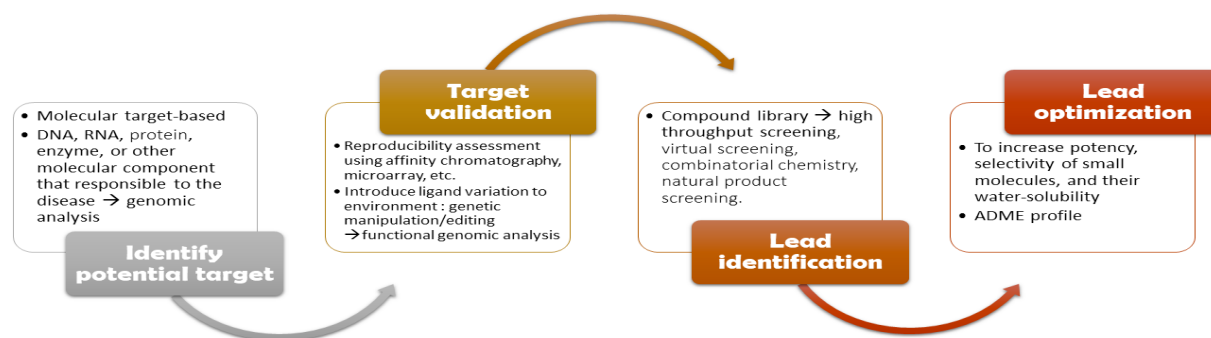


FIGURE 2. Drug discovery process and pharmacogenomic involvement in each step.<sup>12</sup>

The first step in drug discovery is the identification of potential targets.<sup>12</sup> Molecular target-based drug discovery has become the dominant approach after advances in molecular biology have managed to identify potential druggable targets in the human genome.<sup>10</sup> It identifies targets based on identified factors responsible for the disease at the molecular level<sup>13</sup> Protein detection results in new agents involved in disease processes and targets disease-causing processes.<sup>14</sup> Targets are protein related molecules such as DNA, RNA, receptor-like (GPCR), enzymes, and ion channels in addition to chemical compounds with small molecular weights or biological compounds such as antibodies or recombinant proteins.<sup>15,16</sup> The applied approach in identifying targets includes direct biochemical methods, genetic interaction methods, computational methods and some approaches such as bioinformatics to study data mining, genetic polymorphisms and their relationship to disease, expression profiling at the mRNA level, phenotypic and pathway analysis, and function screening.<sup>12</sup> One approach *in silico* study can analyze the gene encoding the

target region based on the tendency of the ligand to bind to the target protein or small drug molecule. So that, it can be anchored in the target structure of a known location,<sup>13</sup> molecular docking can predict patterns of interactions between proteins and small molecules and evaluate the bonds between the two molecules.<sup>17</sup>

After the target has been identified, the next step is target validation to examine whether the molecular target is involved in the disease process and modulating its therapeutic effect. The two main steps in target validation are reproducibility and introducing ligand variations to the environment. Reproducibility can be conducted using various techniques such as affinity chromatography, expression cloning, protein microarray, biochemical suppression, siRNA, and DNA microarray. Introduce ligand variations to the environment based on genetic manipulation of target genes (*in vitro*) such as knock out genes with CRISPR, antibody, a chemical approach to the protein that codes for genome.<sup>12</sup>

The third step is lead identification. It begins with collecting small drug candidate molecules, namely a

compound library.<sup>10</sup> This process can be carried out with the help of technologies such as high throughput screening thereby reducing reagent costs and more practical screening, virtual screening, combinatorial chemistry, and natural product screening.<sup>11</sup>

After identifying the lead compounds, the next important step in drug development is chemical or lead optimization to increase the potency and selectivity of small molecules, water-solubility, properties of ADME (absorption, distribution, metabolism, excretion) and their toxicity profile, involving a series of iterative syntheses and characterization of potential drugs.<sup>10,12</sup> Through structural information of the target protein, computational modelling that describes the interaction between lead compounds and their molecular targets can produce new chemical structures with potentially enhanced binding properties.<sup>10</sup>

Some applications of molecular target-based drug discovery such as protein convertase subtilisin/Kexin type 9 (PCSK9) as a target for the treatment of high cholesterol. In addition, there are aromatase inhibitors for breast cancer, cytochrome P450 family 17 sub-family A member 1 (CYP17A1) inhibitors for prostate cancer, poly (ADP-ribose) polymerase (PARP) inhibitors for ovarian cancer, tyrosine-protein kinase inhibitors erbB-2 (HER2) have also showed clinical responses in certain patient groups. Overexpression of HER2 is associated with a highly aggressive form of breast cancer with an overall poor prognosis.<sup>8</sup> Furthermore, based on its genomic profile such as platelet reactivity candidate gene in clopidogrel targeting the CYP3A4 genotype \*22 and PPAR- $\alpha$  candidate genes (G209A and A208G) and identified a significant association between PPAR- $\alpha$  and decreased platelet activity. Also, drug interactions with genes such as CYP3A5 and tacrolimus in relation to patients expressing the CYP3A5 enzyme (CYP3A5 \*1/\*3 or \*1/\*1) compared to those not

expressing.<sup>2</sup>

The drug discovery process is not developed based on the molecular target of the pathophysiology of a disease only but also be used with a phenotypic screening approach for diseases whose targets have not been known, yet. In phenotypic screening using cell-based assays to determine changes in characteristics associated with disease. For example, using filipin staining to identify compounds that are effective in the treatment of Niemann Pick type C disease where is the active compound will induce some changes such as suppressing the survival of cancer cells and microbial organisms, changes in cell morphology, and functional changes in cells. On the other hand, lead optimization derived from phenotypic screening can be difficult as the molecular target is unknown.<sup>10</sup>

### **Drug repurposing**

One of the effective strategies in drug discovery is using a drug repurposing approach. This approach, also known as drug repositioning, identifies and applies approved drugs to treat a new disease. This approach aims to find new indications quickly by testing a collection of approved drugs. Associated with the discovery of new drugs, repurposing drugs can improve and accelerate the identification of effective drug candidates.<sup>10</sup>

There are two methods of drug repurposing, namely computational and experimental methods. The commonly computational approach that used in drug repurposing are signature-based methods, molecular docking, genetic association, pathway-based methods, retrospective clinical analysis, and novel data resources technique (TABLE 1). While the experimental approach can be conducted in two ways, the first is through phenotypic screening by high throughput screening of compound, the second by performing binding assays to identify target interactions.<sup>18</sup> However, suppose these computational

and experimental tests are successful. In that case, it is unknown how efficient the drug repurposing process will be because it still requires substantive

and time-consuming safety testing, especially if the drug is given to a patient much different from the type of patient previously approved.<sup>19</sup>

TABLE 1. Commonly used-computational approach in drug repurposing

Computational approach	Principle technique
Signature-based methods	Based on a comparison of the unique characteristics of a drug against other drugs and diseases from omics data
Molecular docking	3D-structure-based computational strategy to predict complementarity of binding sites between ligands and therapeutic targets, then calculate their binding affinity.
Genetic association	Analysing disease-associated genes that might be potential drug targets
Pathway-based methods	Based on network analysis between genetic, protein or disease pathway data for re-identify drug targets
Retrospective clinical analysis	Based on systematic analysis of electronic health records, clinical trial database and post-marketing surveillance data
Novel data resources	By genomic database screening to identify potential drug target

### Drug development

Pharmacogenomics has recently become an integral part of the drug development process. Pharmacogenomics reduces drug costs by pharmaceutical companies and innovators around the world as many research and drug development companies basically make mistakes in drug production due to “drugs that can not be used by humans” in the final stages of development. It is considered one of the solutions to do, because it is very financially and scientifically disadvantageous. With the advent of new knowledge about genetic variants/ polymorphisms that can affect drug response or toxicity, these polymorphisms are widely accepted as practical information in the labelling of many drugs, as well as pharmacogenomics. It can provide solutions to these problems.<sup>20</sup>

The main weapon in pharmacogenomics research is genetic testing, which results in haplotypes. What is being tested in pharmacogenomics is a polymorphism in the enzyme that

metabolizes the drug. This haplotype predicts how the effect (phenotype) will result from different haplotypes. The phenotypic spectra generated included poor metabolism, intermediate metabolism, normal metabolism, rapid metabolism, and ultra-rapid metabolism. The type of phenotype produced has a profound effect on drug metabolism in the body, resulting in the effects of the drug on each individual.<sup>21</sup>

Identifying molecules that go from preclinical development to human testing is the basis of the drug development process and involves significant economic cost, time and effort. This first requires a series of experiments to collect sufficient evidence of therapeutic efficacy and safety, studies with so-called healthy and unhealthy human volunteers to determine the efficacy and safety of the drug.<sup>22</sup>

In principle, drug development based on pharmacological genomics is based on drug-metabolizing enzymes (DMEs), and can be divided into two types: broad enzymes and weak enzymes, in addition to normal enzymes. In clinical

trial 1-3, the drug under development will be tested using these two DME samples. DME data is usually collected from a sufficient number of volunteers. In phase 1 clinical trials, the drug will only be tested in vitro and in vivo to see if this DME affects the levels of the drug administered after metabolism. At this stage, the variant data analyzed in the pharmacogenomics test is not yet completely robust unless a lot of prior data has been collected. In phase 2 clinical trials, the drug is tested in humans using a given number of samples, and DME status, drug levels, and drug efficacy are measured in this second clinical trial. If the drug passes clinical trial 2, it will proceed to a phase 3 human clinical trial with a larger sample, but it will be even less robust for performing genome-

wide association studies. In phase 3 clinical trials, the drug is administered first, then the blood concentration of the drug is measured along with the effect of the drug (both main effects and side effects), and then the DME sample gene is detected and measured. The relationship between drug level and its effect will be evaluated. At this phase, it is possible to determine if the drug is suitable for marketing and consumption and has been declared safe. The results obtained from the comparison of pharmacological genomics show that drug developers maximize drug effects and minimize unwanted side effects by regulating the synthesis of drug compounds with DME polymorphisms that occur in some people (FIGURE 3).<sup>23,24</sup>

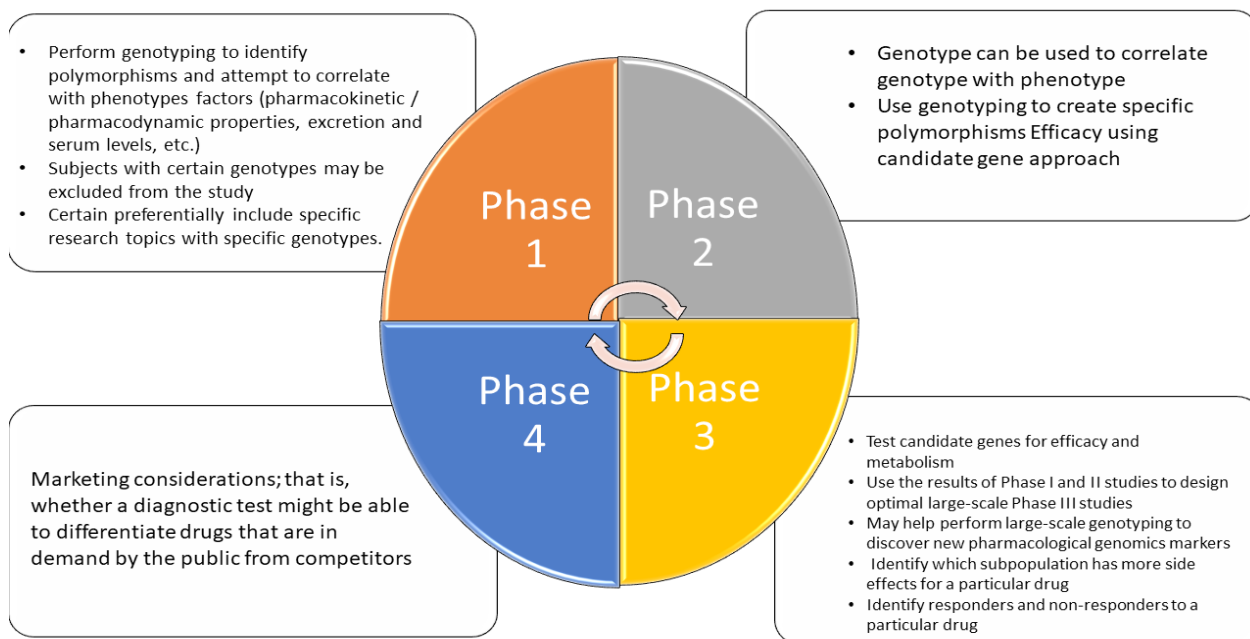


FIGURE 3. Pharmacogenomic in clinical trial phase.<sup>23,24</sup>

A clinical trial 4 or what is commonly referred to as a post-marketing surveillance is a clinical trial conducted after a drug is on the market. This phase focuses on the occurrence of side effects that have not been observed in clinical trials.<sup>23</sup> Occasionally, we may look for other side effects that occur but do not harm the patient (e.g. viagra is basically taking antihypertensive

drugs), but according to clinical trial 4, male vitality boosters or antis. A new effect as an impotence was discovered). Clinical trial 4 typically collects only data on adverse events resulting from all available reports, regardless of the patient's condition or environment. However, in pharmacogenomics, this data is consistent with the patient's DME status. Patients who report side effects

will be asked for permission to detect the gene to determine if the patient has a DME polymorphism. Compared to the side effects that are causing DME data, drug developers can do several things to improve the effectiveness of the drug. If this does not improve, add information to the drug label so that you can continue to use and sell the drug, you don't have to withdraw it first.<sup>25,26</sup>

The development of pharmacogenomics in clinical trial 4 is based on data related to the number of side effects of the drug that occur after the drug is launched, but is unknown in clinical trial, and these side effects are in this drug genomics. Studies that cause a lot of treatment costs are expected to reduce or prevent the side effects of the drug. However, it is difficult for both pharmaceutical companies and clinicians to apply pharmacological genomics studies, and the results are difficult to apply due to lack of reports, and the difficulty of identifying risks is very small. This study is not suitable as a tool for clinical trials or pharmacovigilance. It requires effort, a very long-term solution, and the right way to deal with it.<sup>25</sup>

However, due to the high cost of genetic testing, pharmacogenomics research applies to all drugs on the market worldwide. To date, few drugs have strong cost-effective research evidence, such as abacavir, allopurinol, carbamazepine, and clopidogrel. One of the concerns of cost-effectiveness studies related to this pharmacogenetic study is that each country has many factors such as ethnicity, testing costs, drug costs, etc. However, it is significant between countries/locations where this study is conducted although there is no relationship. The test is conducted for the economical reason. This means that cost-effective results do not vary significantly between countries, regardless of where this pharmacological genomics study is conducted.<sup>21</sup>

An example of a drug that has

benefited from this pharmacogenomics study and can be clinically tested is acetaminophen. Paracetamol/acetaminophen is one of the most widely distributed and used medicines worldwide. Although paracetamol acts as both an analgesic and an antipyretic, it is widely used, but paracetamol has been found to be a fourth-order analgesic that causes allergies to patients. Paracetamol is metabolized in the body by many enzymes such as UGT1A6, UGT1A1, UGT1A9, and UGT2B15, which convert paracetamol to paracetamol glucuronide. The enzymes SULT1A1, SULT1A3, SULT1A4, SULT1E1 and SULT2A1 then convert paracetamol to paracetamol sulfate. Similar to cytochrome enzymes such as CYP2E1, CYP1A2, CYP2A6, CYP2D6, CYP3A4 that oxidize paracetamol.<sup>27,28</sup>

Of the three enzymes listed above, CYPs produce a metabolite, also known as acetaminophen (N-acetylbenzoquinone-imine) or NAPQI. In people with normal metabolic enzymes, this NAPQI metabolite does not circulate well in the blood and does not cause allergies, but in enzyme polymorphisms, the number of NAPQIs increases significantly and causes allergies. There are not only rapidly developing type 1 allergies such as urticaria, angioedema, and anaphylaxis, but also late-stage allergies that appear years later. In addition to the cytochrome enzyme that produces NAPQI metabolites, there are other enzymes that metabolize NAPQI in a non-reactive form that does not cause allergies: the GSTM1, GSTT1, and GSTP1 enzymes. Polymorphisms in this enzyme affect the metabolic activity of NAPQI, leading to the development of allergic effects.<sup>27,29</sup> Drug mixing studies can instantly identify polymorphisms in CYP and GST enzymes, minimizing side effects and allergies experienced by patients, thus reducing treatment costs. It greatly improves the efficiency of mass processing.<sup>27</sup>

## **Challenges of pharmacogenomic implementation in population**

Pharmacogenomics provides a better option for patients, especially patients with gene differentiation, so drugs can be adapted to the patient's genomic conditions. However, there are many challenges in implementing pharmacogenomics for drug development. The first challenge is the lack of pharmacogenomics knowledge among health workers themselves. Most health workers know that pharmacogenomics helps improve therapeutic outcomes but realize that they lack information and knowledge on implementing it. A study in the United States reported only 12.6% of health workers are very familiar with pharmacogenomics. Therefore healthcare professionals need individualized training or courses to understand and apply pharmacogenomics to their patients. In addition, the lack of consensus guidelines for genetic testing and implementation may present additional hurdles for clinicians seeking to apply pharmacogenomics to routine clinical practice.<sup>30</sup>

The second challenge is the lack of technology to apply pharmacogenomics, as it is known that pharmacogenomics is based on the state of individual genes. Therefore, before applying pharmacogenomics, tools to identify the patient's genes are needed. Obviously these tools are expensive and not all institutions can offer them. With the exception of equipment, the laboratories used to inspect samples related to pharmacogenomics testing cannot provide results. In the United States, the Clinical Laboratory Improvement Amendments (CLIA) publishes specific standards for laboratories that test human specimens for diagnosis, prevention, and treatment. If the laboratory is not CLIA certified and does not meet the requirements of the analytical criteria, the results published

by that laboratory should not be used as the basis for clinical decision making, but only as exploratory. It should be interpreted.<sup>23,31</sup>

The third challenge is drug modification of the patient's gene detection results. Once the patient's genes are discovered, the next step is to adjust the treatment (drug) to the patient's genomic composition. This makes it difficult for many healthcare professionals to use because there is a lot of information that needs to be processed and translated to change the drug. In such a condition, if the patient's clinical condition improves, the treatment will eventually return to the previous mode based on the patient's clinical data and the drug will be declared successful. Moreover, it is difficult to carry out pharmacological genomics studies involving many ethnic groups in the world.<sup>23</sup>

The fourth challenge is the value of money. As explained in the first and second challenges, the application of this pharmacogenomics requires sufficient knowledge and skill. Obtaining training, courses, and gene tracking tools can be very expensive and it is often questioned whether the high costs are related to the effectiveness of the treatment. In addition, any type of drug needs to be adjusted to identify the patient's genes. In the first place, treatment attempts tend to be "failed" or "invalid." This actually increases treatment costs and is inefficient for both the healthcare facility and the patient himself.<sup>31</sup>

The fifth issue is related to ethical issues. An ethical issue of concern in pharmacogenomics is the privacy or confidentiality of the subject. Participants must be fully informed about how genetic material is handled, how genetic testing is performed, how data is used, where genetic samples are stored, and the security of the DNA bank that stores the genetic material. Attention should be paid to those who have access to this genetic material. In addition, you need to be informed that DNA may be needed



for future use and how this data will be stored. Education and informed consent for future use should also be given in advance.<sup>32,33</sup>

## CONCLUSION

At present, pharmacogenomic has significant role in drug discovery and development. Pharmacogenomic leads to precision medicine that expect to be more efficient, beneficial, and safe therapeutic strategy. Nevertheless, there were many obstacles to implement pharmacogenomic in clinical practices, especially due to resources and ethical issues. There must be collaboration between scientist, physicians, and government to support pharmacogenomic research for better pharmacotherapy in the future.

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